Dalle sulfoniluree ai nuovi farmaci ipoglicemizzanti: luci ed ombre nel trattamento del paziente diabetico con comorbidità cardiovascolari

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Malattia Cardiovascolare nel diabete di tipo 2

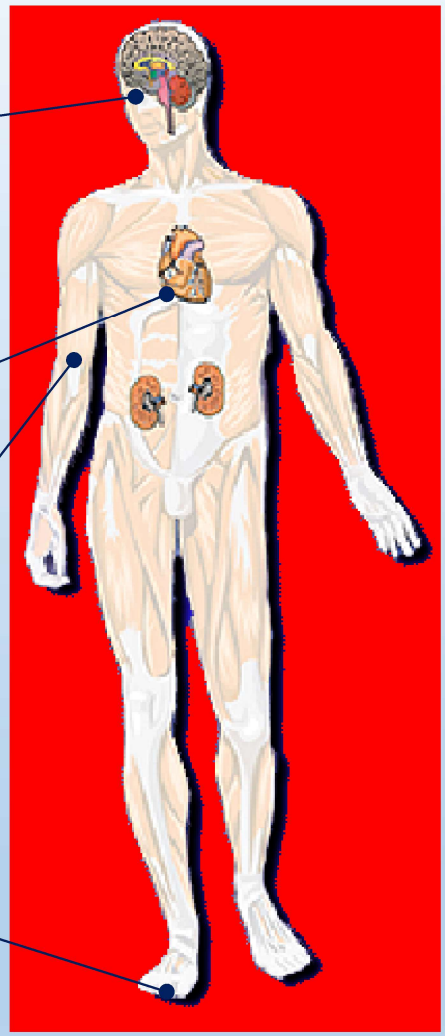
Prevalenza

7% — **Malattia Cerebrovascolare (1)**

18%

35% — **Ipertensione(2)**

4.5% — **Claudicatio Intemittens(1)**



STROKE: rischio aumentato da 2 a 3 volte*

S.C.A.: rischio aumentato da 1.5 a 3-4 volte*

Mortalità: 2 volte ♂ 4 volte ♀

Rischio amputazione aumentato di 15 volte*

***in confronto alla popolazione generale**

1. Wingard DL *et al. Prevalence of cardiovascular and renal complications in older adults with normal or impaired glucose tolerance or NIDDM. A population-based study.* Diabetes Care 1993; 16: 1022-25.
2. UKPDS 6. Diabetes Res 1990; 13: 1–11. 3. Balkau B *et al*. Lancet 1997; 350: 1680. 4. King's Fund. Counting the Cost. BDA, 1996.

TRIALOGUEPLUS

Focus sul Paziente Iperglicemico a Rischio Cardiovascolare

Progetto realizzato da

AMD - ANMCO - FADOI - SID

Il progetto Trialogue Plus è stato realizzato con il contributo incondizionato di SANOFI

1 – Percorso Assistenziale Diabetologico/Metabolico

TRIALOGUEPLUS
Focus sul Paziente Iperglicemico a Rischio Cardiovascolare

TERAPIA FARMACOLOGICA

- **TERAPIA IPOGLICEMIZZANTE**

*Dati recenti indicano che la terapia insulinica con analogo a lunga durata d'azione (**glargine**) è efficace e sicura nel trattamento dell'iperglicemia nei diabetici di tipo 2, anche al di fuori della fase acuta di malattia.*

*Nello studio **ORIGIN**, infatti, i pazienti trattati con **glargine** non presentavano né un aumento degli eventi CV né un aumento dell'incidenza di neoplasie.*

Il progetto Trialogue Plus è stato realizzato con il contributo incondizionato di SANOFI

Basal Insulin and Cardiovascular and Other Outcomes in Dysglycemia

The ORIGIN Trial Investigators

N Engl J Med 2012; 367:319-328J

Obiettivi dello studio

Endpoint co-primari

- Composito di morte CV, IM non fatale, ictus non fatale
- Composito di morte CV, IM non fatale, ictus non fatale, procedure di rivascolarizzazione o ospedalizzazione per scompenso cardiaco

Endpoint secondari

- Composito microvascolare (inclusi retinopatia diabetica o nefropatia)
- Sviluppo di diabete di tipo 2 in pazienti con disglicemia
- Mortalità per tutte le cause

Endpoint di tollerabilità

- Tutti gli eventi avversi, inclusi episodi ipoglicemici e insorgenza di cancro

The ORIGIN Trial

Endpoint primario

- Si è evidenziato per glargine un effetto neutro sugli outcome CV, in quanto non vi è stata né una riduzione nè un incremento degli eventi, (primo endpoint co-primario HR 1.02 : 95% CI 0.94-1.11 p=0.63; secondo endpoint co-primario HR 1.04 : 95% CI 0.97-1.11 p=0.27)

Endpoint secondario

- Non si sono evidenziate differenze negli eventi micro vascolari tra i due gruppi di trattamento (HR 0.97: 95% CI 0.90–1.05; p=0.43)
- Insulina glargine ha ridotto nei pazienti con pre-diabete la progressione a diabete del 28% (p=0.006)
- Non si è rilevata una differenza nell'incidenza di mortalità per tutte le cause (HR 0.98: 95% CI 0.90–1.08; p=0.70)

1 – Percorso Assistenziale Diabetologico/Metabolico

TRIALOGUEPLUS
Focus sul Paziente Iperglicemico a Rischio Cardiovascolare

TERAPIA FARMACOLOGICA

- **TERAPIA IPOGLICEMIZZANTE**

- **Raccomandazione 11**

  Tra gli ipoglicemizzanti orali, la **metformina** è il farmaco di prima scelta, salvo controindicazioni. In aggiunta a metformina, tutti i farmaci antidiabetici possono essere utilizzati, tenendo conto del fenotipo del paziente (terapia personalizzata) e dei possibili effetti collaterali.

- **Raccomandazione 12**

  Evitare l'uso di secretagoghi a lunga emivita come la glibenclamide, soprattutto nei pazienti anziani, con pregressi eventi CV o altre comorbilità.

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1 – Percorso Assistenziale Diabetologico/Metabolico

TERAPIA FARMACOLOGICA

- **TERAPIA IPOGLICEMIZZANTE**

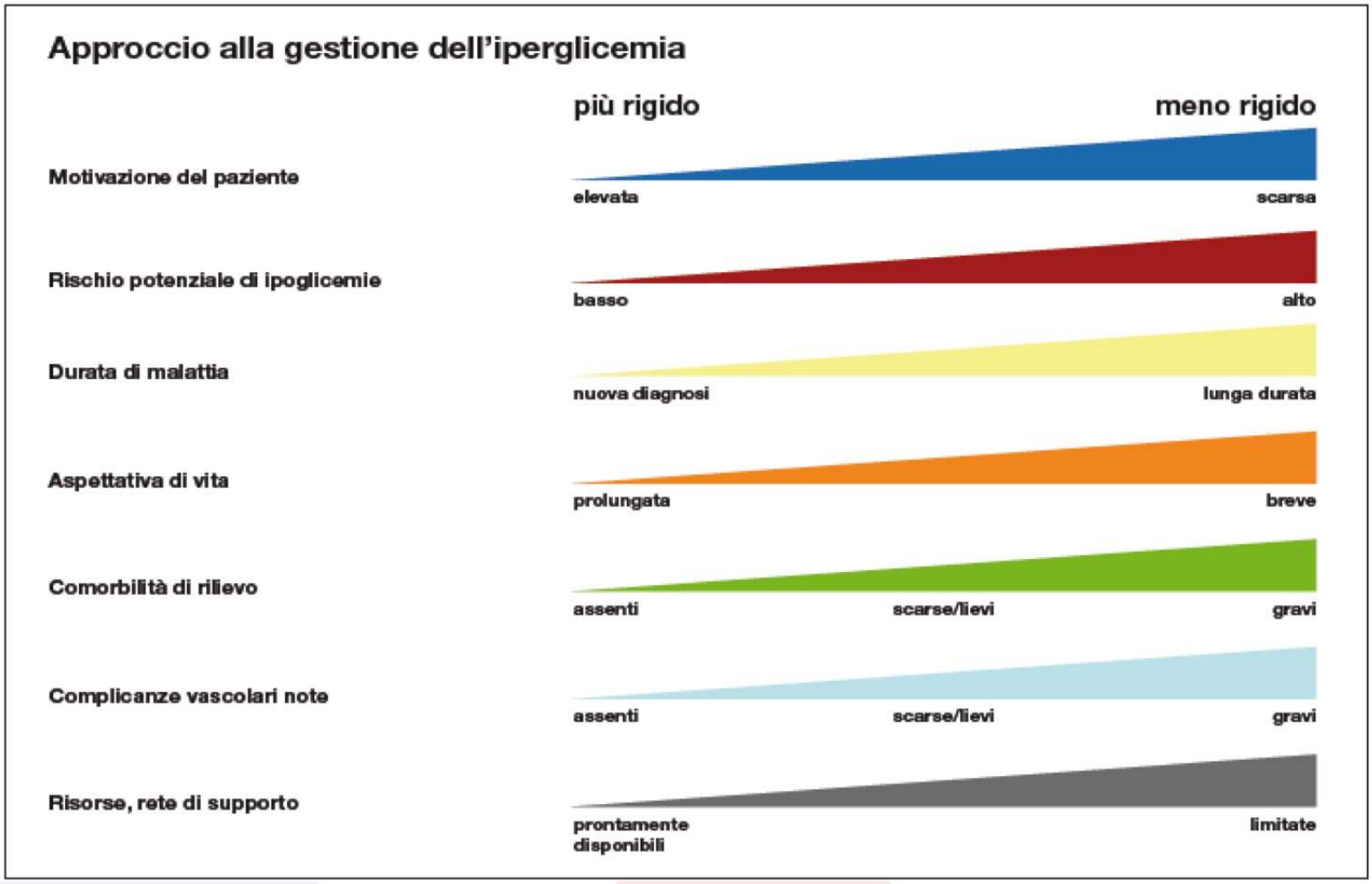
*Tutti i farmaci ipoglicemizzanti possono essere utilizzati per il raggiungimento degli obiettivi glicemici a meno che non sussistano controindicazioni specifiche. In caso di esami con mezzo di contrasto, la **metformina** deve essere sospesa 24 ore prima e ripresa dopo 48 ore, previo controllo della creatinina ematica. Il **pioglitazone** è controindicato nel paziente con scompenso cardiaco, qualunque sia la Classe NYHA (I-IV), nel paziente con carcinoma vescicale anamnestico, in fase attiva o con macroematuria e nel paziente a rischio di frattura .*

*Gli inserimenti terapeutici successivi alla metformina devono **tener conto del fenotipo del paziente** (presenza di sovrappeso/obesità, prevalenza di deficit secretivo, di insulino resistenza o di iperglicemia post-prandiale) e di possibili effetti favorevoli aggiuntivi di alcune classi di farmaci (minor rischio di ipoglicemie, riduzione o almeno mantenimento del peso corporeo).*

Il progetto Trialogue Plus è stato realizzato con il contributo incondizionato di SANOFI

1 – Percorso Assistenziale Diabetologico/Metabolico

TRIALOGUEPLUS
Focus sul Paziente Iperglicemico a Rischio Cardiovascolare



Il progetto Trialogue Plus è stato realizzato con il contributo incondizionato di SANOFI

ACCORD, ADVANCE, VADT: cosa ci dicono ?

- **Il trattamento intensivo della glicemia ci può dare risultati positivi in pazienti:**

  - ***con età < 65 anni***
  - ***in discreto compenso metabolico HbA1c ≤ 8%***
  - ***senza precedenti CVD***
  - ***con storia di malattia < 10 anni***

Riduzione dell'iperglicemia e complicanze vascolari nel diabete di tipo 2

	Microvascolari	Macrovascolari
Diabete all'esordio	**Beneficio**	**Beneficio**
Diabete di lunga durata	**Beneficio**	**No beneficio** **Possibile danno**

FDA 2008 – Valutazione del rischio cardiovascolare per le nuove terapie anti-diabetiche per il trattamento del DMT2

- **Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes**

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H. N Engl J Med 2007; 356:2457-2471

- In the rosiglitazone group, as compared with the control group, the odds ratio for myocardial infarction was 1.43 (95% confidence interval [CI], 1.03 to 1.98; P=0.03), and the odds ratio for death from cardiovascular causes was 1.64 (95% CI, 0.98 to 2.74; P=0.06).
- Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance. Our study was limited by a lack of access to original source data, which would have enabled time-to-event analysis. Despite these limitations, patients and providers should consider the potential for serious adverse cardiovascular effects of treatment with rosiglitazone for type 2 diabetes.
- The odds ratio for death from any cause was 1.18 (95% CI, 0.89 to 1.55; P = 0.24).

December 2008 FDA Guidance on Evaluating CV Risk in New Antidiabetic Therapies for T2DM

Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

Upper bound of 2 – sided 95% confidence interval for estimated CV risk

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2008
Clinical/Medical

III. RECOMMENDATIONS

To establish the safety of a new antidiabetic therapy to treat type 2 diabetes, sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk. To ensure that a new therapy does not increase cardiovascular risk to an unacceptable extent, the development program for a new type 2 antidiabetic therapy should include the following.

For new clinical studies in the planning stage:

- Sponsors should establish an independent cardiovascular endpoints committee to prospectively adjudicate, in a blinded fashion, cardiovascular events during all phase 2 and phase 3 trials. These events should include cardiovascular mortality, myocardial infarction, and stroke, and can include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possibly other endpoints.

- Sponsors should ensure that phase 2 and phase 3 clinical trials are appropriately designed and conducted so that a meta-analysis can be performed at the time of completion of these studies that appropriately accounts for important study design features and patient or study level covariates. To obtain sufficient endpoints to allow a meaningful estimate of risk, the phase 2 and phase 3 programs should include patients at higher risk of cardiovascular events, such as patients with relatively advanced disease, elderly patients, and patients with some degree of renal impairment. Because these types of patients are likely to be treated with the antidiabetic agent, if approved, this population is more appropriate than a younger and healthier population for assessment of other aspects of the test drug's safety.

- Sponsors also should provide a protocol describing the statistical methods for the proposed meta-analysis, including the endpoints that will be assessed. At this time, we believe it would be reasonable to include in a meta-analysis all placebo-controlled trials, add-on trials (i.e., drug versus placebo, each added to standard therapy), and active-

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf

FDA 2008 – Valutazione del rischio cardiovascolare per le nuove terapie anti-diabetiche per il trattamento del DMT2

- Questa linea guida richiede agli Sponosor di dimostrare che **le nuove terapie per il DMT2 non comportino un incremento del rischio cardiovscolare inaccettabile**.

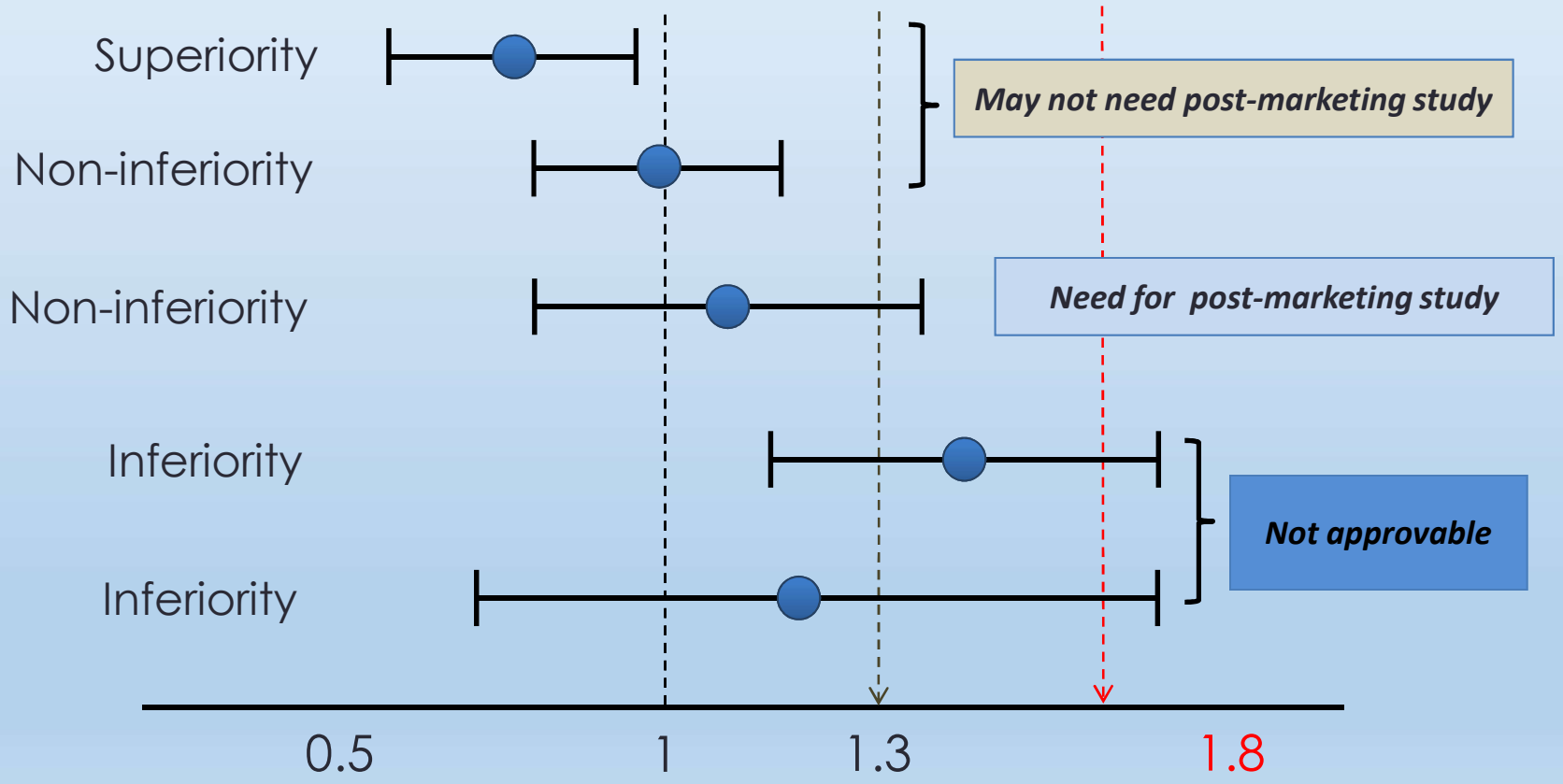
- La linea guida stabilisce che **per supportare l'approvazione di un farmaco,** lo Sponsor deve confrontare l'incidenza degli eventi CV maggiori ottenuta con il farmaco in studio con l'incidenza dello stesso tipo di eventi ottenuta con il gruppo di confronto e dimostrare che **il limite superiore dell'intervallo di confidenza al 95% a due code del rapporto tra rischi è inferiore a 1.8**

- Se questo limite **è compreso tra 1.3 e 1.8** e il rapporto rischio-beneficio globale del farmaco è a supporto dell'approvazione allora è necessario uno studio cardiovascolare post-marketing per dimostrare **definitivamente** che questo limite superiore **è inferiore a 1.3**

- Queste raccomandazioni specificano inoltre:
  - **arruolamento di soggetti ad alto rischio**
  - **minima esposizione del trattamento di 18-24 mesi**
  - **aggiudicazione degli eventi CV in cieco e centralizzata**
  - **un numero sufficiente di eventi da escludere un incremento del rischio pari al 30%**

Guidance for industry: diabetesmelitus-evaluating cardiovascular risk in new antidiabetic therapies to treat type2 diabetes. 2008.

FDA criteria for assessing CV safety



Glucose-lowering Drugs in T2DM: Some Major Clinical Trials

Acronym	Tested Agents	Outcome	Status
Insulin			
ORIGIN	Insulin Glargine vs standard	CV death, MI, Stroke	**Reported**
DEVOTE	Insulin Degludec vs Glargine	CV death, MI, Stroke	Ongoing
DPP-4 inhibition			
SAVOR-TIMI 53	Saxagliptin vs placebo	CV death, MI, Stroke	**Reported**
EXAMINE	Alogliptin vs placebo	CV death, MI, Stroke	**Reported**
TECOS	Sitagliptin vs placebo	CV death, MI, UA, Stroke	**Reported**
CAROLINA	Linagliptin vs glimepiride	CV death, MI, UA, Stroke	Ongoing
CARMELINA	Linagliptin vs placebo	CV death, MI, UA, Stroke	Ongoing
OMNEON	Omaragliptin vs placebo	CV death, MI, UA, Stroke	Ongoing
GLP-1 agonism			
ELIXA	Lixisenatide vs placebo	CV death, MI, UA, Stroke	**Reported**
REWIND	Dulaglutide vs placebo	CV death, MI,, Stroke	Ongoing
LEADER	Liraglutide vs placebo	CV death, MI, Stroke	Ongoing
EXSCEL	Exenatide Wkly vs placebo	CV death, MI, Stroke	Ongoing
SUSTAIN 6	Semaglutide vs placebo	CV death, MI, Stroke	Ongoing
FREEDOM-CVO	Exenatide vs placebo	CV death, MI, UA, Stroke	Ongoing
SGLT2 inhibition			
EMPA-REG OUTCOME	Empagliflozin vs placebo	CV death, MI, UA, Stroke	**Reported**
DECLARE-TIMI 58	Dapagliflozin vs placebo	CV death, MI, Stroke	Ongoing
CANVAS	Canagliflozin vs placebo	CV death, MI, UA, Stroke	Ongoing
CREDENCE	Canagliflozin vs placebo	CV, Renal death, ESRD, 2XCr	Ongoing

CARDIOVASCULAR SAFETY OF SULFONYLUREAS

Sulfonylureas, while promoting release of insulin[1-2] and through blockade of metabolism regulated adenosine triphospate–sensitive potassium channels (K_{ATP}) present in pancreatic b-cell membranes, also block K_{ATP} channels present in cardiac cells and coronary vasculature[3-4]. This action impairs ischemic preconditioning and prevents coronary vasodilation in response to ischemia[5-10].

1. Panten U, Schwanstecher M, Schwanstecher C. Sulfonylurea receptors and mechanism of sulfonylurea action Exp Clin Endocrinol Diabetes, 104 (1996), pp. 1–9
2. Groop L. Sulphonylureas in NIDDM. Diabetes Care, 15 (1992), pp. 737–754
3. Edwards G, Weston A. The pharmacology of ATP-sensitive potassium channels Annu Rev Pharmacol Toxicol, 33 (1993), pp. 597–637
4. Terzic A, Jahangir A, Kurachi Y. Cardiac ATP-sensitive K^+ channels: regulation by intracellular nucleotides and potassium opening drugs Am J Physiol, 38 (1995), pp. C525–C545
5. Findlay I. Inhibition of ATP-sensitive K^+ channels in cardiac muscle by the sulphonylurea drug glibenclamide J Pharmacol Exp Ther, 261 (1992), pp. 540–545
6. Cleveland JCJr, Meldrum DR, Cain BS, Banerjee A, Harkem AH. Oral sulfonylurea hypoglycemic agents prevent ischemic preconditioning in human myocardium: two paradoxes revisited Circulation, 96 (1997), pp. 29–32
7. Gross GJ. ATP-sensitive potassium channels and myocardial preconditioning Basic Res Cardiol, 90 (1995), pp. 85–88
8. Jackson WF. Arteriolar tone is determined by activity of ATP-sensitive potassium channels. Am J Physiol, 265 (1993), pp. H1797–H1803
9. Narishige T, Egashira K, Akatsuka Y, Takahashi T, Kasuya H, Takeshita A. Glibenclamide prevents coronary vasodilation induced by β1-adrenoceptor stimulation in dogs Am J Physiol, 266 (1994), pp. H84–H92
10. Murray C, Jennings R, Reimer K. Preconditioning with ischemia: a delay in lethal injury in ischaemic myocardium Circulation, 74 (1986), pp. 1124–1136

CARDIOVASCULAR SAFETY OF SULFONYLUREAS

- Other mechanisms by which sulfonylureas may increase mortality in patients with MI include inhibition of the endogenous fibrinolytic system. This could be effected through enhanced production of proinsulin, which is known to stimulate endothelial production of plasminogen activator inhibitor-1 [1-2].
- The blockade of potassium channels also promotes myocardial refractoriness, possibly predisposing to arrhytmias[3].
- Glibenclamide also blocks mitochondrial ATP-sensitive K^+ channels in cardiac myocytes, resulting in the inhibition of ischemic preconditioning[4].

1. T.K Nordt, H Sawa, S Fujii, B.E Sobel. Induction of plasminogen activator inhibitor type-1 (PAI-1) by proinsulin and insulin in vivo. Circulation, 91 (1995), pp. 764–770
2. T.K Nordt, D.J Schneider, B.E Sobel Augmentation of the synthesis of plasminogen activator inhibitor type-1 by precursors of insulin. A potential risk factor for vascular disease Circulation, 89 (1994), pp. 321–330
3. Pogatsa G. Potassium channels in the cardiovascular system. Diabetes Res Clin Pract 1995; 157: 181-8
4. Sato T, Nishida H, Miyazaki M, Nakaya H. Effects of sulfonylureas on mitochondrial ATP-sensitive K+ channels in cardiac myocytes: implications for sulfonylurea controversy. Diabetes Metab Res Rev. 2006; 22(5):341-7

CARDIOVASCULAR SAFETY OF SULFONYLUREAS

The optimal mode of coronary revascularization for diabetics

A risk-adjusted long-term study comparing coronary angioplasty and coronary bypass surgery

O'Keefe JH et al, *Eur Heart J* (1998) 19:1696–703

La differenza di sopravvivenza fra PTCA e CABG si verifica solo nei pazienti diabetici trattati con SU.

I fattori di rischio per aumentata mortalità intra ospedaliera dopo angioplastica per IMA sono risultati:

- LVEF < 40%,
- Pregressa CABG,
- Età,
- Trattamento con SU.

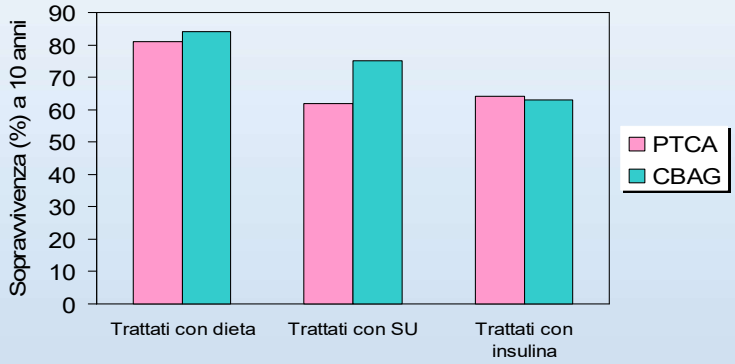
Sulfonylurea drugs increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction.

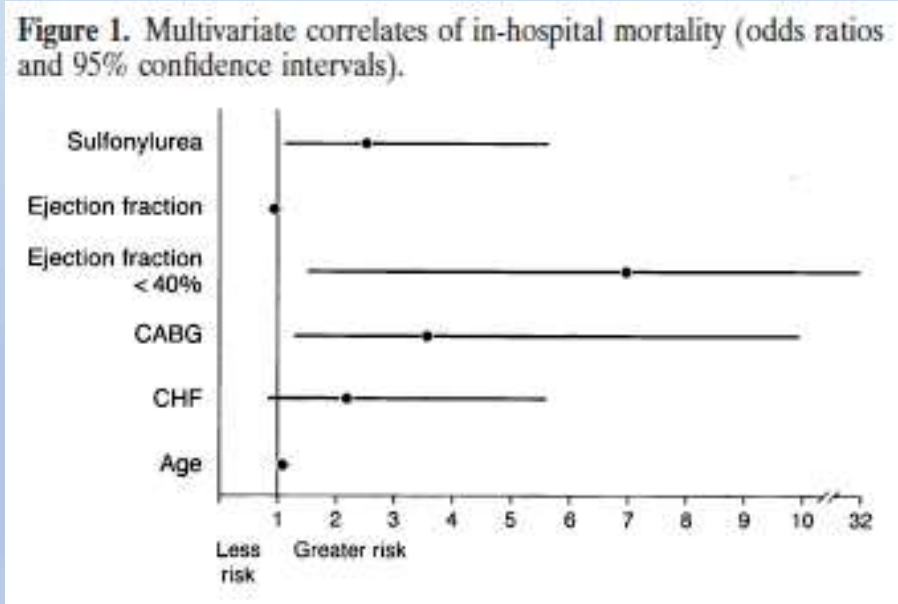
- Sulfonylurea drug use is associated with an increased risk of in-hospital mortality among diabetic patients undergoing coronary angioplasty for acute myocardial infarction. This early risk is not explained by an increase in ventricular arrhythmias, but may reflect deleterious effects of sulfonylurea drugs on myocardial tolerance for ischemia and reperfusion

- **Most recent reports, however, have challenged these conclusions**.

- Congestive heart failure, but **not sulfonylurea drug use**, was associated with an increased incidence of **in-hospital ventricular arrhythmias**.

- Congestive heart failure, prior bypass surgery and female gender, but not sulfonylurea drug use, were associated with **late adverse events**.





Garratt KN et al, *Eur Heart J* (1999) 33:119–24

CARDIOVASCULAR SAFETY OF SULFONYLUREAS

In the French nationwide registry on Acute ST-elevation and non ST-elevation Myocardial Infarction (FAST-MI), no hazard was associated with the use of SUs before the acute episode[1].

- ✓ Mortality was lower in patients previously treated with SUs (3.9%) vs. those on other oral medications (6.4%), insulin (9.4%), or no medication (8.4%) (P = 0.014).
- ✓ In addition, patients previously receiving gliclazide/glimepiride had improved in-hospital outcomes, compared with those on glibenclamide[1].
- ✓ In-hospital complications were similar in patients treated with gliclazide or glimepiride, for either arrhythmias (occurrence of atrial fibrillation, ventricular fibrillation, sustained ventricular tachycardia, or atrioventricular block: gliclazide, 6.3% vs. glimepiride, 9.7%, P = 0.30) or ischemic complications (reinfarction or stroke: gliclazide, 3.4% vs .glimepiride, 5.2%, P=0.41), or mortality (gliclazide, 3.8% vs. glimepiride, 1.5%, P 0.33), or any of the above complications (gliclazide, 12.0% vs. glimepiride, 14.9%, P = 0.51).
- ✓ In contrast, in-hospital complications, including hospital mortality, significantly differed for patients on pancreatic cell-specific Sus (2,7%), compared with those on glibenclamide (7,5%) (P = 0,019).

1. Zeller M(1), Danchin N, Simon D, Vahanian A, Lorgis L, Cottin Y, Berland J, Gueret P, Wyart P, Deturck R, Tabone X, Machecourt J, Leclercq F, Drouet E, Mulak G, Bataille V, Cambou JP, Ferrieres J, Simon T; French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction investigators. Impact of Type of Preadmission Sulfonylureas on Mortality and Cardiovascular Outcomes in Diabetic Patients with Acute Myocardial Infarction. J Clin Endocrinol Metab. 2010 Nov;95(11): 4993-5002

CARDIOVASCULAR SAFETY OF SULFONYLUREAS

- In diabetic patients with acute MI, the first Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction randomized trial (**DIGAMI**) documented improved outcomes in patients who received insulin, when compared with controls who were probably mostly treated with Sus[1].

- In contrast, in the United Kingdom Prospective Diabetes Study (**UKPDS**), treatment with SU was not associated with higher rates of cardiovascular complications[2].

- Reassuring results as to the safety of SUs were also reported in patients who survived an acute MI. In **the population-based Olmsted County cohort study**, mortality was not statistically different in 46 patients receiving SU compared with 56 receiving insulin, during a mean follow-up of 2.7 yrs. after acute MI. During follow-up (mean 2.762.3 years, maximum 8.4 years), a total of 24 deaths occurred in the sulfonylurea group versus 20 in the insulin group. Of these, 12 deaths were attributable to cardiac causes in the sulfonylurea group versus 10 in the insulin-treated group (differences not significant: P = 0.79 for overall survival and P= 0.54 for survival to cardiac death [Kaplan-Meier estimates])[3].

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2. United Kingdom Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352:837–853
3. Brady PA, Al-Suwaidi J, Kopecky SL, Terzic A. Sulfonylureas and mortality in diabetic patients after myocardial infarction Circulation 1998; 97:709–710

CARDIOVASCULAR SAFETY OF SULFONYLUREAS

- Klamann et al. found no increase in hospital mortality in 76 patients admitted for acute MI while on SUs, compared with 89 diabetic patients without SUs[1].

- In patients receiving thrombolysis from a multicenter trial, Halkin et al. found that the 121 diabetic patients treated with SU had no increased in-hospital or 1-yr mortality; survival appeared lower in diabetic patients previously treated with insuli2[2].

- More recently a post hoc analysis from the Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction-2 (**DIGAMI-2**) trial showed that, patients discharged on SUs had no increased risk of stroke or recurrent MI (HR 0.81, 95% CI 0.57-1.14; P = 0.23), contrary to patients on insulin, (HR 1.73, 95% CI 1.26-2.37; P = 0.0007) [3].

- The Action in Diabetes and Vascular Disease trial (**ADVANCE STUDY**) showed that gliclazide treatment used to achieve intensive glucose control was associated with a decreased rate of primary endpoints at 5 yr, combining major macrovascular and microvascular events (18.1%, vs. 20.0% with standard control; hazard ratio, 0.90; 95% confidence interval [CI], 0.82 to 0.98; P=0.01), as well as that of major microvascular events (9.4% vs. 10.9%; hazard ratio, 0.86; 95% CI, 0.77 to 0.97; P=0.01), primarily because of a reduction in the incidence of nephropathy (4.1% vs 5.2%; hazard ratio, 0.79; 95% CI, 0.66 to 0.93; P=0.006)[4].

1. Klamann A, Sarfert P, Launhardt V, Schulte G, Schmiegel WH, Nauck MA. Myocardial infarction in diabetic vs non-diabetic subjects. Survival and infarct size following therapy with sulfonylureas (glibenclamide). Eur Heart J 2000; 21:220–229
2. Halkin A, Roth A, Jonas M, Behar S. Sulfonylureas are not associated with increased mortality in diabetics treated with thrombolysis for acute myocardial infarction. J Thromb Thrombolysis 2001; 12:177–184
3. Mellbin LG, Malmberg K, Norhammar A, Wedel H, Ryde I. The impact of glucose lowering treatment on long-term prognosis in patients with type 2 diabetes and myocardial infarction: a report from the DIGAMI 2 trial. Eur Heart J 2008; 29:166–176
4. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F, ADVANCE Collaborative Group 2008 Intensive blood glucose control and vascular outcomes in patients with type2 diabetes. N Engl J Med 2008; 358:2560–2572

CARDIOVASCULAR SAFETY OF SULFONYLUREAS

- Observational studies in diabetic patients on chronic therapy have suggested that patients treated with either glimepiride or gliclazide had lower long-term mortality than patients receiving glibenclamide [1-2].

- A case-control study from the large North Jutland County registry showed that, compared with non diabetic patients, subjects treated with older Sus (glibenclamide, tolbutamide, or glipizide) had a greater risk of MI than patients treated with newer SUs (gliclazide or glimepiride) [respectively, OR 2.07 (95% CI 1.81–2.37) vs. 1.36 (95% CI 1.01–1.84)][3] .

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2. Monami M, Luzzi C, Lamanna C, Chiasserini V, Addante F, Desideri CM, Masotti G, Marchionni N, Mannucci E 2006 Three year mortality in diabetic patients treated with different combinations of insulin secretagogues and metformin. Diabetes Metab Res Rev 2006; 22:477–482
3. Johnsen SP, Monster TB, Olsen ML, Thisted H, McLaughlin JK, Sørensen HT, Lervang HH, Rungby J 2006 Risk and short-term prognosis of myocardial infarction among users of antidiabetic drugs. Am J Ther 13:134–140

CARDIOVASCULAR SAFETY OF SULFONYLUREAS

- Glibenclamide is shown to be harmful to patients with type 2 diabetes mellitus and CAD, even when combined with metformin, and avoiding the drug is suggested in such high-risk patients[1].

- A retrospective cohort study involving 11,141 patients with type 2 diabetes mellitus revealed no significant difference in overall mortality with the use of glipizide, glyburide, or glimepiride monotherapy, **but the study did find a non significant trend towards increased overall mortality with glyburide and glipizide vs glimepiride in patients with documented CAD**[2].

- Glibenclamide is associated with increased cardiovascular mortality and morbidity in patients with diabetes mellitus undergoing emergent percutaneous coronary intervention after myocardial infarction. Cox proportional hazard regression analyses adjusted for age, sex, calendar year, comorbidity and concomitant pharmacotherapy showed an increased risk of cardiovascular mortality (HR 2.91, 95% confidence interval [CI] 1.26-6.72 ; p=0.012), with glibenclamide compared to metformin[3].

1. Fisman EZ, Tenenbaum A. A cardiologic approach to non-insulin antidiabetic pharmacotherapy in patients with heart disease. *Cardiovasc Diabetol*. 2009 Jul 20;8:38.
2. Pantalone KM, Kattan MW, Yu C, et al. The risk of overall mortality in patients with type 2 diabetes receiving glipizide, glyburide, or glimepiride monotherapy: a retrospective analysis. *Diabetes Care*. 2010 Jun;33(6):1224–1229
3. Jørgensen CH, Gislason GH, Bretler D, Sørensen R, Norgaard ML, Hansen ML, Schramm TK, Abildstrom SZ, Torp-Pedersen C, Hansen PR. Glyburide increases risk in patients with diabetes mellitus after emergent percutaneous intervention for myocardial infarction--a nationwide study. Int J Cardiol. 2011 Nov 3;152(3):327-31.

Nuovi farmaci per la cura del diabete, con particolare riferimento a incretino-mimetici (DPP-4 i e GLP-1 a.) e gliflozine (SGLT-2 i)

Aggiornamento di Novembre 2015

A cura del Gruppo multidisciplinare sui farmaci per il diabete
Regione Emilia-Romagna

In base ai risultati di una recente revisione sistematica della letteratura (RS) condotta dall'OMS ai fini dell'aggiornamento della Lista dei Farmaci Essenziali, l'uso di glibenclamide sembra essere associato ad un aumentato rischio di ipoglicemie nei pazienti con più di 60 anni [WHO 2013]; la **glibenclamide non è quindi raccomandata nei pazienti con età >60 anni**.

Azione della metformina sulle complicanze macrovascolari

- Nello Studio **UKPDS** in un gruppo di 342 pazienti don DMT2 obesi o in sovrappeso, il trattamento con metformina ha ridotto del **36% la mortalità globale** (95% CI 9-55, **p= 0,011**) e del **39% il rischio di infarto del miocardio rispetto al trattamento convenzionale** (**p= 0,01**) e ha ridotto del **41% il rischio di ictus rispetto al trattamento intensivo (insulinico o con sulfonilurea)** (p= 0,03), mentre la riduzione del rischio cardiovascolare **non raggiungeva la significatività statistica nei soggetti in trattamento intensivo** (insulinico o con suilfonilurea).
- Nello stesso gruppo si è osservata un riduzione non significativa delle complicanze microvascolari (p 0,19)[1].

1. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998 Sep 12;352(9131):854-65

Azione della metformina sulle complicanze macrovascolari

- A smaller study using metformin as an add-on to insulin confirmed as a secondary endpoint that **the drug reduced the risk of macrovascular disease after a follow-up period of 4.3 years** (hazard ratio, 0.61 (95% CI, 0.40-0.94; P =0.02)[1].

- A Meta-regression showed a significant correlation of the effect of metformin on cardiovascular events with trial duration and with minimum and maximum age for inclusion, meaning that the drug appeared to be **more beneficial in longer trials enrolling younger patients**. It is likely that metformin monotherapy is associated with improved survival (MH-OR: 0.801[0.625-1.024], p = 0.076)[2].
- However, concomitant use with **sulphonylureas** was associated with reduced survival (MH-OR: 1.432[1.068-1.918], p = 0.016) [2].

1. Lamanna C, Monami M, Marchionni N, Mannucci E. Effect of metformin on cardiovascular events and mortality: a meta-analysis of randomized clinical trials Diabetes Obes Metab. 2011 Mar;13(3):221-8.
2. Kooy A, de Jager J, Lehert P, et al. Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. *Arch Intern Med*. 2009 Mar 23;169(6):616–625.

Diabete tipo 2, studio PROACTIVE

(**PRO**spective pioglit**A**zone **C**linical **T**rial In macro**V**ascular **Events**)

- **Riduzione statisticamente non significativa (10%) dell'end-point composito primario:**

morte per tutte le cause, infarto miocardico non fatale e ictus non fatale, sindrome coronarica acuta, intervento di rivascolarizzazione cardicaca, amputazione maggiore, intervento di rivascolarizzazione agli arti inf.

- **Riduzione statisticamente significativa (16%) per l'end point composito secondario principale (HR** 0.84, 0.72-0.98, p=0.027**):**

morte per tutte le cause, infarto miocardico non fatale e ictus non fatale

- **Riduzione statisticamente significativa di altri 2 end point secondari:**

recidiva di IMA (HR 0.72, 95% CI 0,52-0,99; p=0,045) e recidiva di ictus (HR 0.53, 95% CI 0.34–0.85; p=0.009)

1. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, Skene AM, Tan MH, Lefèbvre PJ, Murray GD, Standl E, Wilcox RG, Wilhelmsen L, Betteridge J, Birkeland K, Golay A, Heine RJ, Korányi L, Laakso M, Mokán M, Norkus A, Pirags V, Podar T, Scheen A, Scherbaum W, Schernthaner G, Schmitz O, Skrha J, Smith U, Taton J; PROactive Investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macrovascular Events): a randomised controlled trial. Lancet. 2005 Oct 8;366(9493):1279-89
2. Wilcox R, Bousser M-G, Betteridge DJ etal, PROactive Investigators. Effects of pioglitazone in patients with type 2 diabetes with or without previous stroke: results from PROactive (PROspective pioglitazone Clinical Trial in macroVascular Events 04). Stroke 2007; 38: 865–873.

Ten-year observational follow-up of the PROACTIVE study[1]

- **In seguito alla sospensione del pioglitazone morbidità e mortalità cardiovascolari sono risultate sovrapponibili nel gruppo precedentemente trattato con pioglitazone rispetto al gruppo placebo per quanto riguarda sia l'end point primario che gli end point secondari - fatta eccezione per una riduzione significativa degli interventi di amputazione maggiore** (RR 0,77, 95% CI 0.57 – 1,05, p= 0,0460).

- **Anche se il pioglitazone è associato ad un incremento del rischio di scompenso cardiaco, è verosimile che ciò sia dovuto alla slatentizzazione di una preesistente insufficienza cardiaca a causa della ritenzione idrica indotta dal pioglitazone piuttosto che ad un effetto diretto sula funzionalità del miocardio.**

- **Durante un follow-up di 10 anni è stata osservata un trend verso una riduzione dell'incidenza di carcinoma della vescica** (RR 0.65, 95% CI 0.33–1.28) **ed un trend verso un incremento dell'incidenza di carcinoma della prostata** (RR 1.47, 95% CI 0.93–2.34).

1. Erdmann E, Harding S, Lam H, Perez A. Ten-year observational follow-up of PROactive: a randomized cardiovascular outcomes trial evaluating pioglitazone in type 2 diabetes. Diabetes Obes Metab. 2016 Mar;18(3):266-73

The possible role of DPPIV in the pathophysiology of HF

- Several stimuli may increase the activity and abundance of both soluble and cardiac DPPIV in HF during the acute and/or chronic stages of this syndrome. High DPPIV activity may reduce the biological activity of peptides with cardio-, vaso- and renoprotective actions including glucagon-like peptide-1 (GLP-1), brain natriuretic peptide (BNP), and stromal cell-derived factor-1 α (SDF-1α) leading to poorer cardiovascular outcomes.

- In addition to its exopeptidase activity, DPPIV also functions as a binding protein. In the renal proximal tubule, DPPIV interacts with the Na+/H+ exchanger isoform 3 protein (NHE3). NHE3 plays a critical role in sodium reabsorption, extracellular volume homeostasis and blood pressure control. DPPIV inhibition reduces NHE3 activity in vitro and in vivo, underscoring the possible role of DPPIV in fluid retention.

- On the other hand, the protease activity of DPPIV can be beneficial for the cardiovascular system by cleaving neuropeptide Y (NPY) and peptide YY (PYY).

Salles TA, dos Santos L, Barauna VG, Girardi AC. Potential role of dipeptidyl peptidase IV in the pathophysiology of heart failure. Int J Mol Sci. 2015 Feb 16;16(2):4226-49

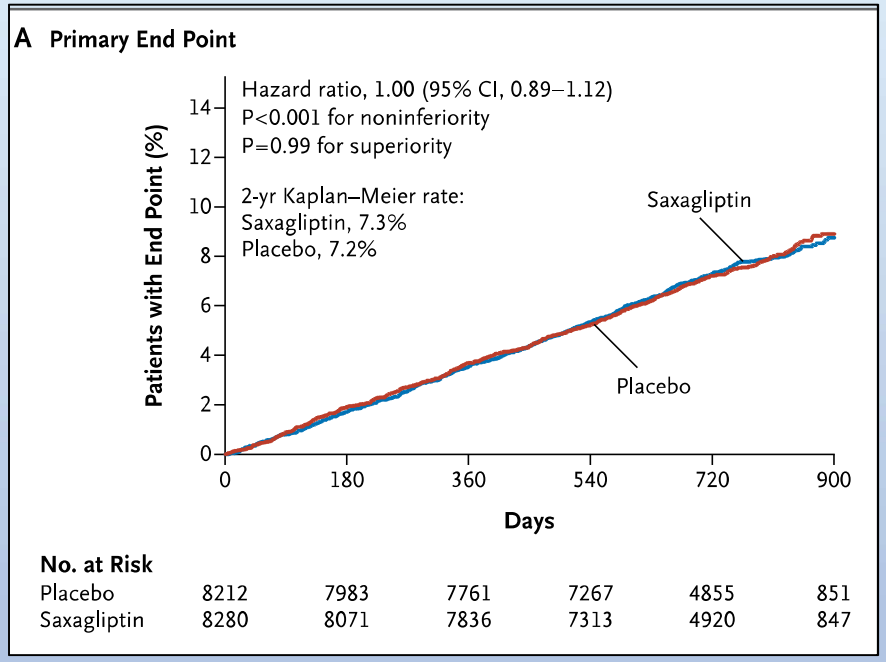
The NEW ENGLAND JOURNAL of MEDICINE
N ENGL J MED 369;14 NEJM.ORG OCTOBER 3, 2013

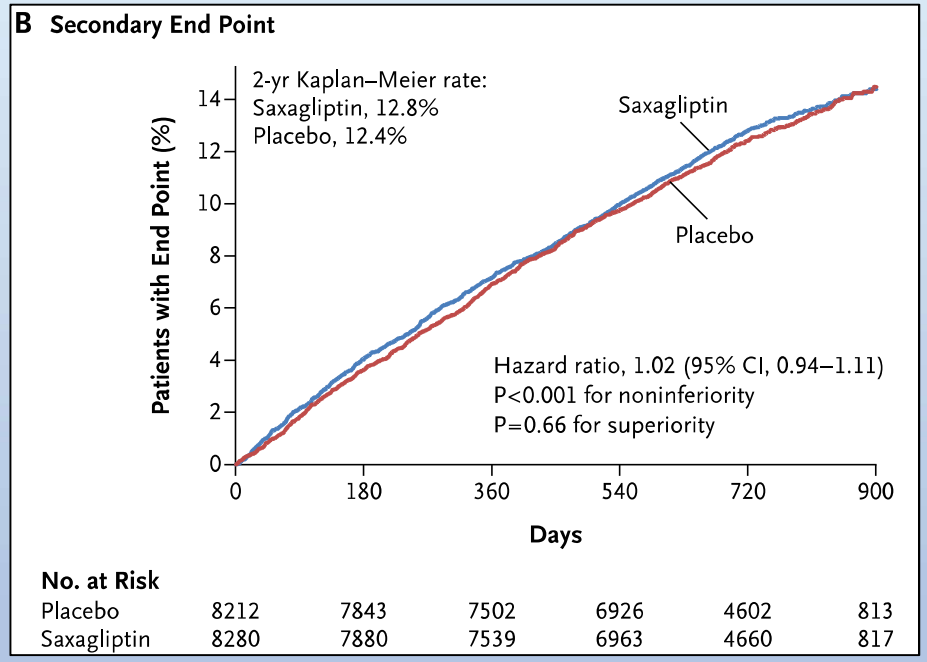
ORIGINAL ARTICLE

Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus

SAVOR-TIMI 53

Pz 16492 con follow up di 2.1 a

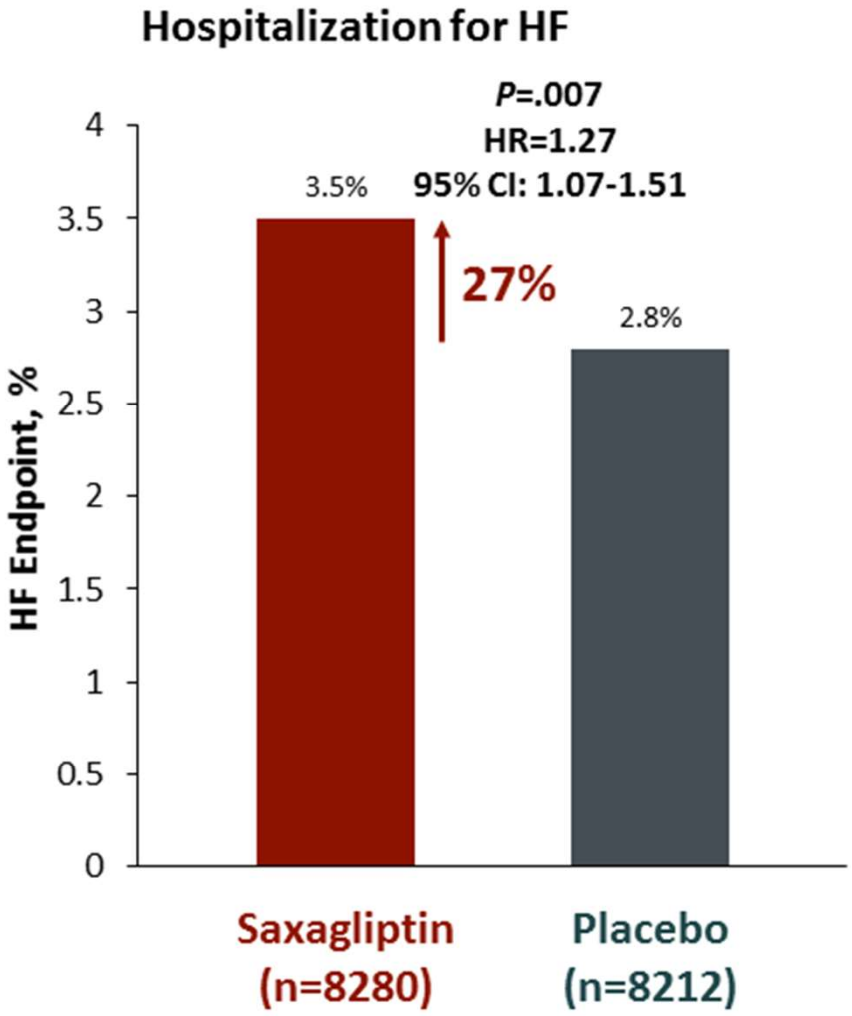




Morte cardiovascolare, IMA e STROKE non fatale

Morte cardiovascolare, IMA e STROKE non fatale, ospedalizzazione per angina instabile, rivascolarizzazione coronarica e scompenso cardiaco

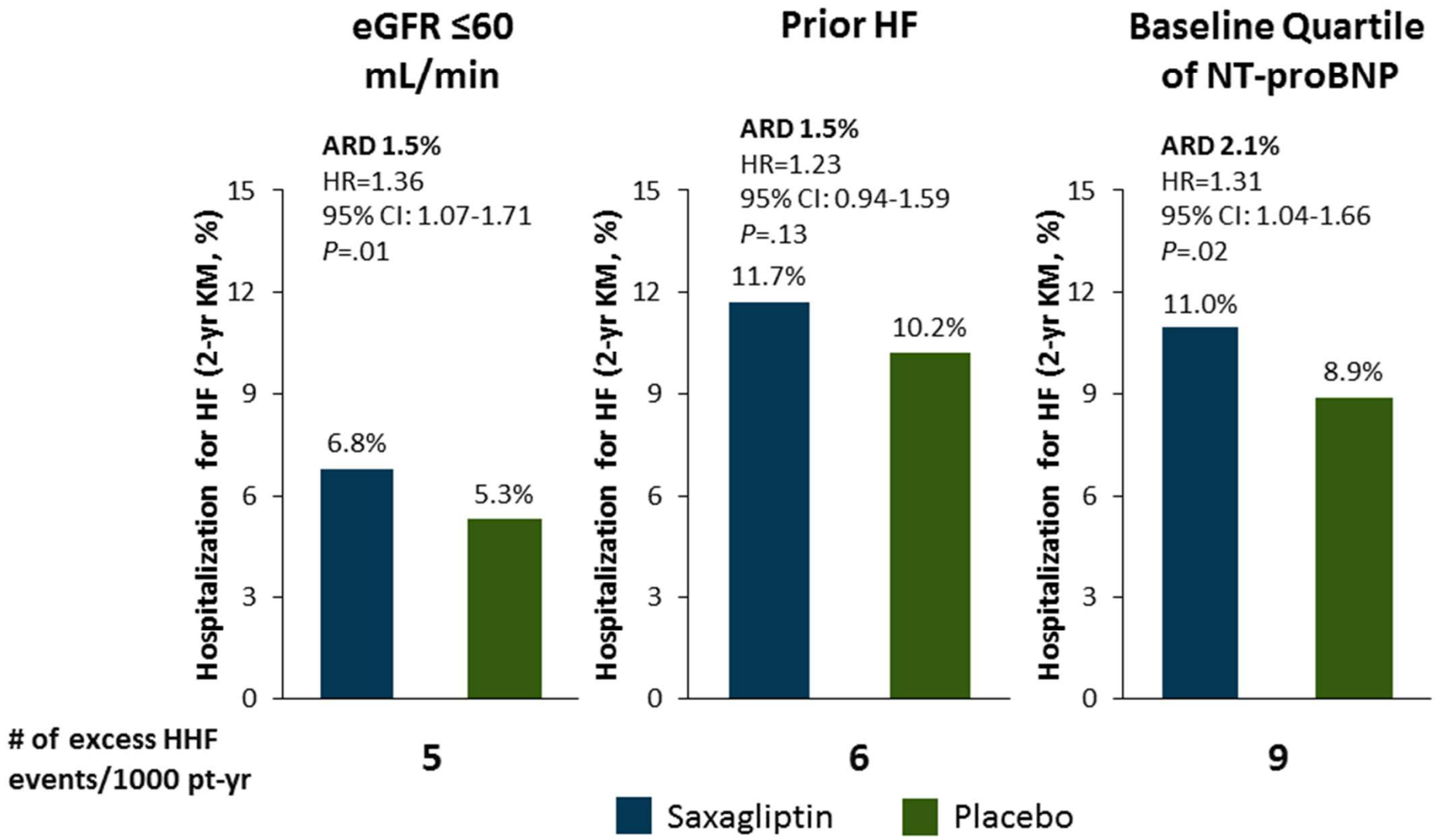
SAVOR-TIMI 53: Hospitalization for HF



Baseline	Saxagliptin (n=8280)	Placebo (n=8212)
Prior HF no. (%)	1056 (12.8)	1049 (12.8)

Scirica BM, et al. *N Engl J Med*. 2013;369:1317-1326.

SAVOR-TIMI 53: Patients at Risk for HF



Scirica BM, et al. *Circulation*. 2014;130:1579-1588.

The NEW ENGLAND JOURNAL of MEDICINE

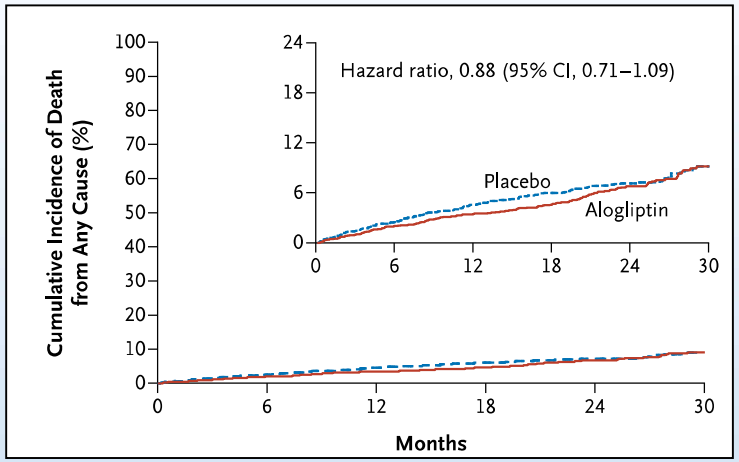
N ENGL J MED 369;14 NEJM.ORG OCTOBER 3, 2013

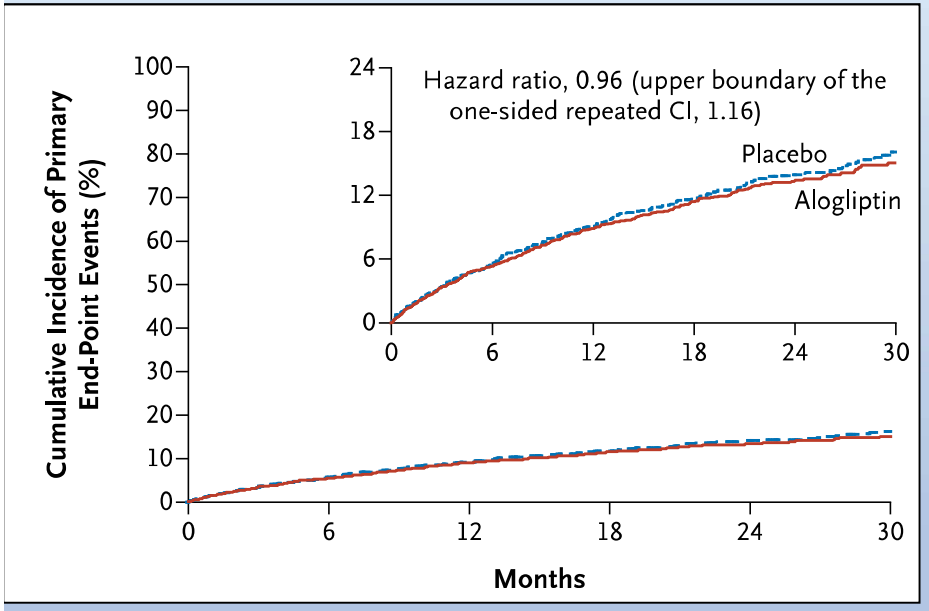
ORIGINAL ARTICLE

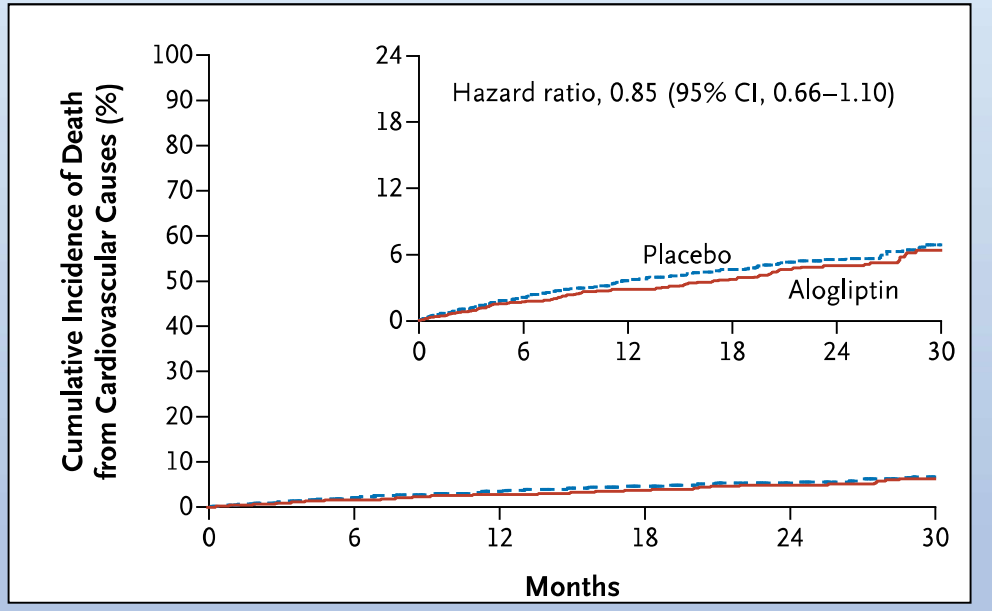
Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes

EXAMINE

Pz 5380 follow up 18 mesi



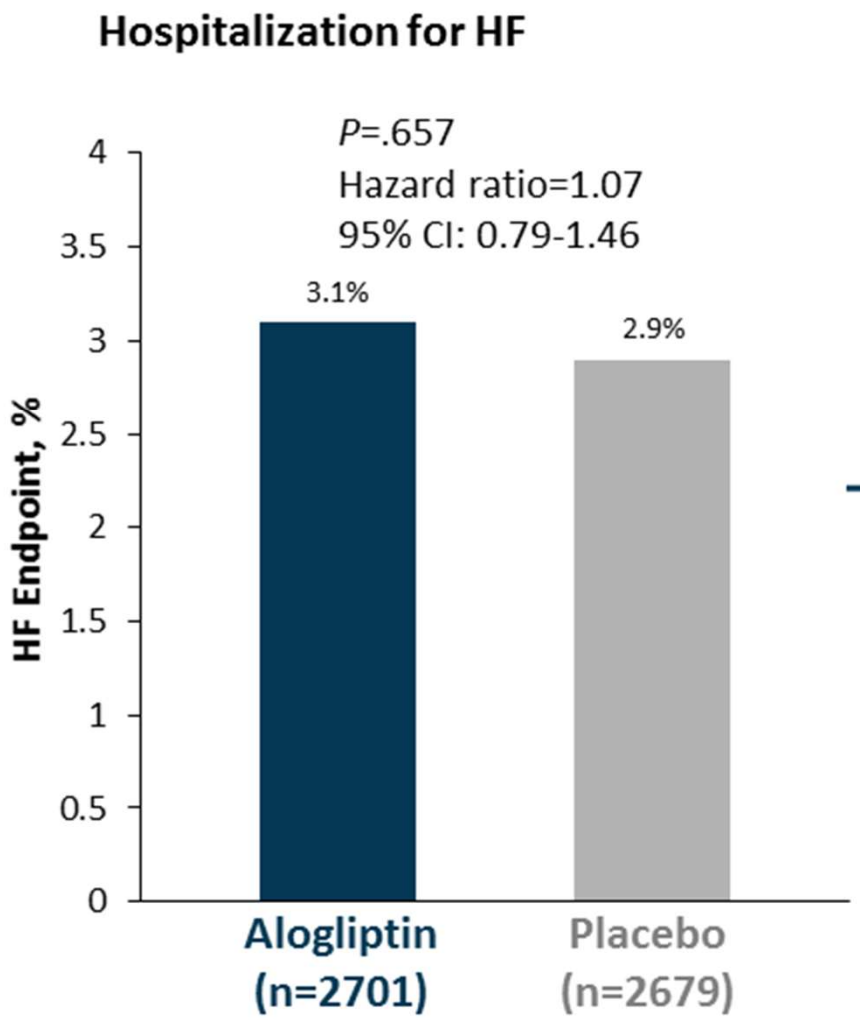




Primary endo point: Morte cardiovascolare, IMA e Stroke non fatali

Secondary end point: Morte cardiovascolare, IMA e Stroke non fatali e rivascolarizzazione urgente per angina instabile nelle prime 24 ore successive al ricovero ospedaliero

EXAMINE: Hospitalization for HF



Baseline	Alogliptin (n=2701)	Placebo (n=2679)
CHF no.(%)	757 (28.0)	744 (27.8)

Zannad F, et al. *Lancet*. 2015;385:2067-2076.
White WB, et al. *N Engl J Med*. 2013;369:1327-1335.

EXAMINE

Pz 5380 follow up 18 mesi

THE LANCET
2015 May 23; 385(9982): 2067-76

Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial

Zannad F, Cannon CP, Cushman WC, Bakris GL, Menon V, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Lam H, White WB; EXAMINE Investigators.

Alogliptin had no effect on composite events of cardiovascular death and hospital admission for heart failure in the post hoc analysis (HR 1·00, 95% CI 0·82-1·21) and results did not differ by baseline BNP concentration. NT-pro-BNP concentrations decreased significantly and similarly in the two groups.

EXAMINE

Pz 5380 follow up 18 mesi

THE LANCET

2015 May 23; 385(9982): 2067-76

Zannad F, Cannon CP, Cushman WC, Bakris GL, Menon V, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Lam H, White WB; EXAMINE Investigators.

Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial

- In the lower-risk subgroup of patients without a history of heart failure at baseline, there was also **no increased risk of the composite endpoint of cardiovascular death and hospital admission for heart failure for alogliptin versus placebo** - Hazard ratio (95% CI) 1·14 (0·85 –1·54), p value 0·337 - although there was a **small absolute increase in hospital admission for heart failure for alogliptin versus placebo** (**0·9**%) - Hazard ratio (95% CI) 1·76 (1·07–2·90), p value 0·026
- However, in this same group of patients, cardiovascular-death rates were nominally lower in those taking alogliptin - Hazard ratio (95% CI) 0·92 (0·64–1·32) p value 0·643 and diuretic use was not increased compared with placebo.
- Hence, on the basis of this evidence, the finding of a higher rate of hospital admission for heart failure with alogliptin in patients without a history of heart failure at baseline could be due to chance.

The NEW ENGLAND JOURNAL of MEDICINE

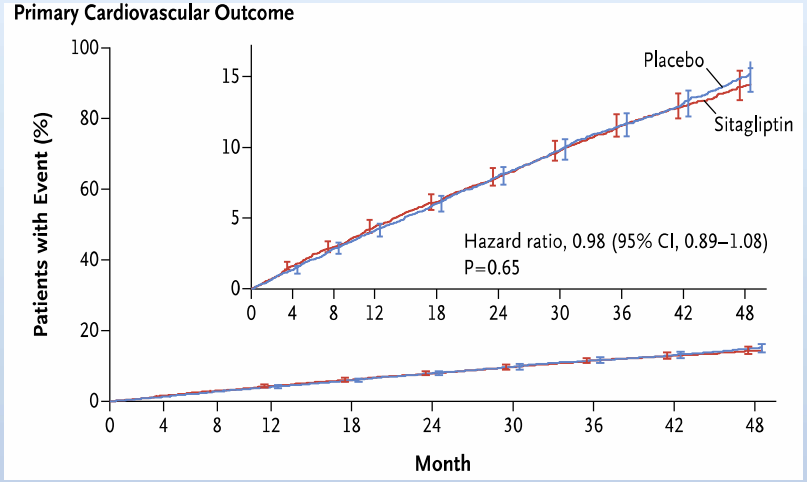
N ENGL J MED 373;3 NEJM.ORG JULY 16, 2015

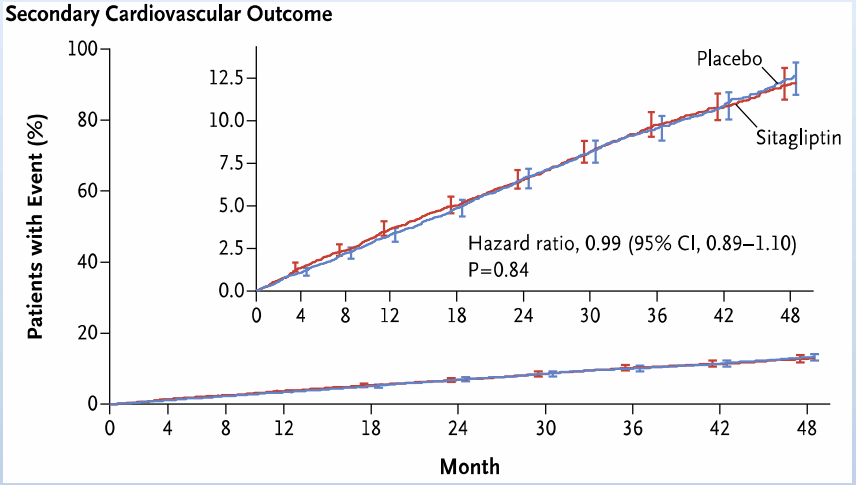
ORIGINAL ARTICLE

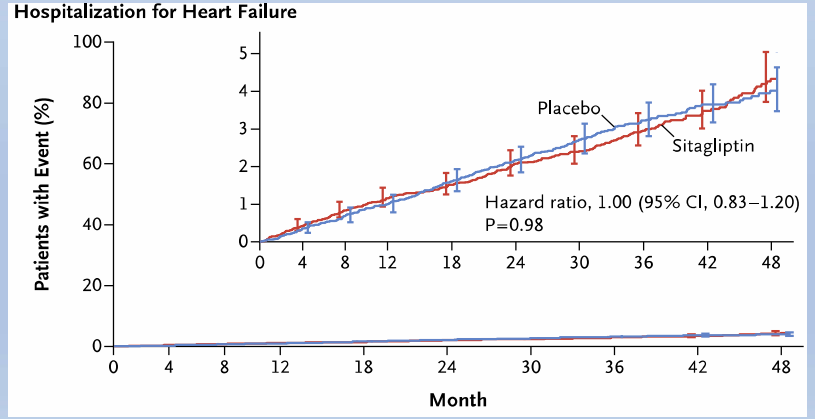
TECOS

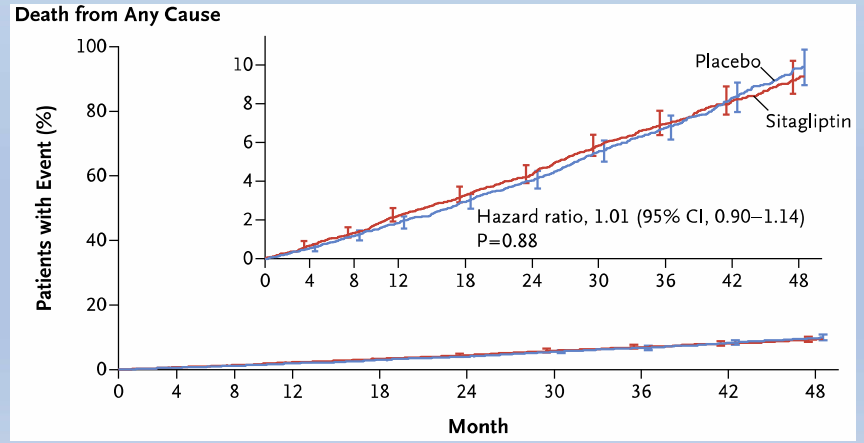
Pz 14671 follow up di 3 a

Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes



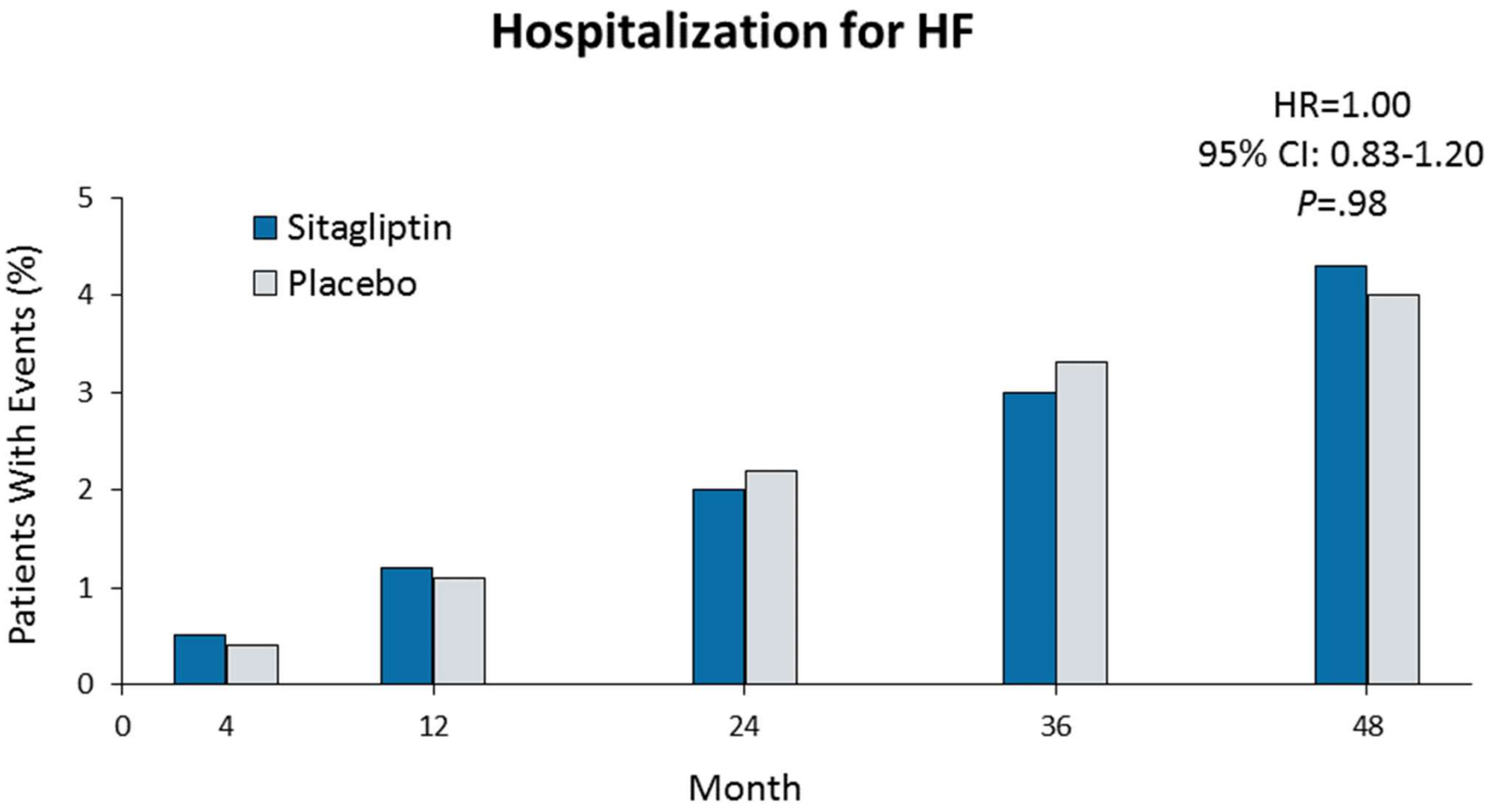






Endpoint composito primario: Morte cardiovascolare, IMA e Stroke non fatali e ospedalizzazione per angina instabile

TECOS: Hospitalization for HF



Green JB, et al. *N Engl J Med*. 2015;373:232-242.

FDA Drug Safety Communication: FDA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing saxagliptin and alogliptin

[4-5-2016] A U.S. Food and Drug Administration (FDA) safety review has found that type 2 diabetes medicines containing saxagliptin and alogliptin may increase the risk of heart failure, particularly in patients who already have heart or kidney disease.

As a result, we are adding new warnings to the drug labels about this safety issue. Saxagliptin and alogliptin are part of the class of dipeptidyl peptidase-4 (DPP-4) inhibitor drugs, which are used with diet and exercise to lower blood sugar in adults with type 2 diabetes.

Patients taking these medicines should contact their health care professionals right away if they develop signs and symptoms of heart failure such as:

Unusual shortness of breath during daily activities
Trouble breathing when lying down
Tiredness, weakness, or fatigue
Weight gain with swelling in the ankles, feet, legs, or stomach

Patients should not stop taking their medicine without first talking to their health care professionals.

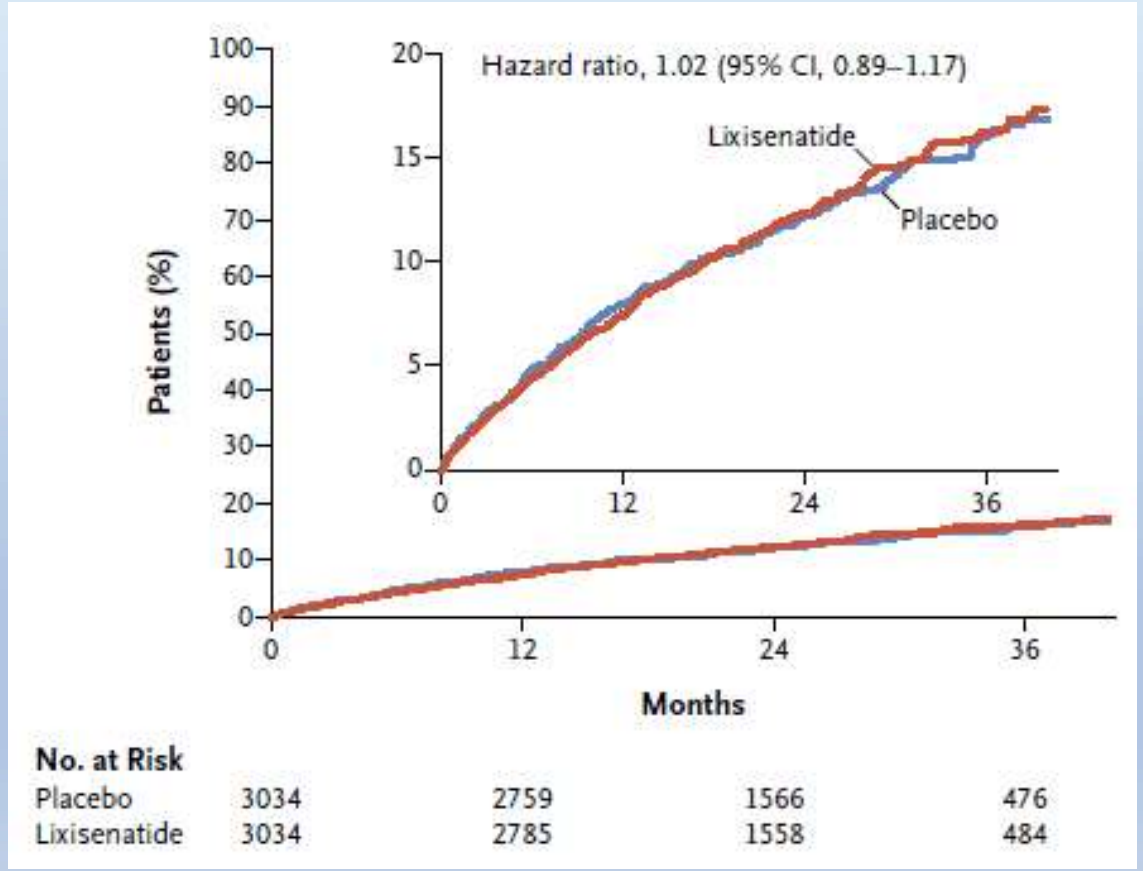
Health care professionals should consider discontinuing the medicine in patients who develop heart failure and monitor their diabetes control.

The NEW ENGLAND JOURNAL of MEDICINE

N ENGL J MED 373;23 NEJM.ORG DECEMBER 3, 2015

ORIGINAL ARTICLE

Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome



No. at Risk				
Placebo	3034	2759	1566	476
Lixisenatide	3034	2785	1558	484

ELIXA

Pz 6068 follow up 2.1 a

Primary end point: morte cardiovascolare, IMA, Stroke e ospedalizzazione per angina instabile

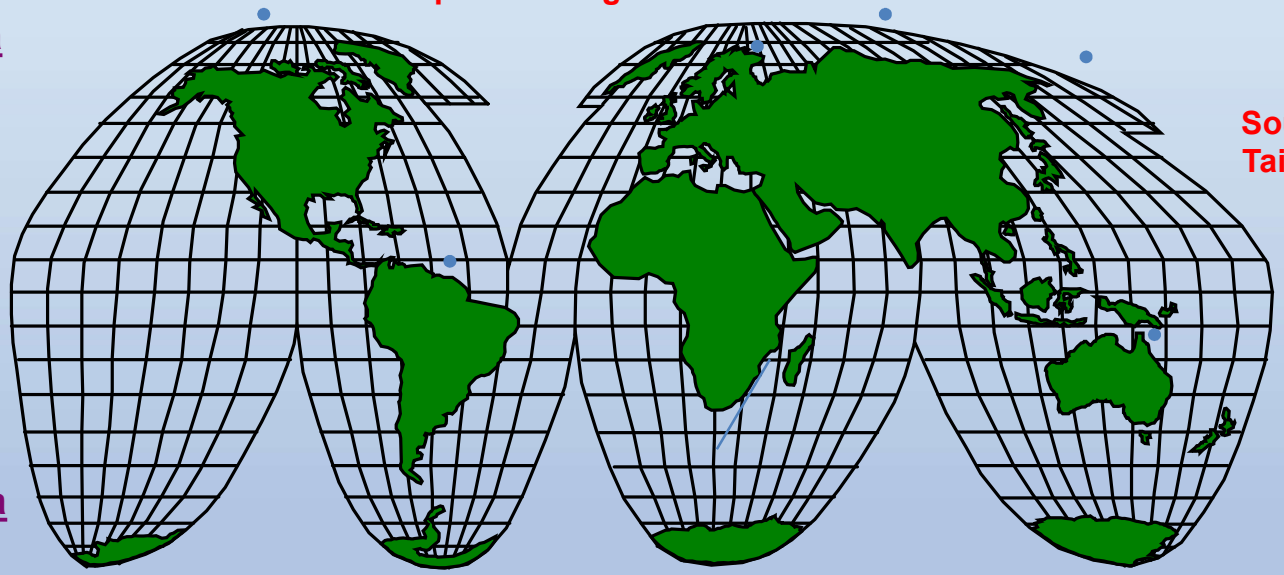
Evaluation of LIXisenatide in Acute Coronary Syndrome
Centri partecipanti nel mondo

49 Paesi
800+ centri
6000 + pazienti

Northern & Southern Europe
NL/Belgium
UK / Sweden / Denmark /
Norway / Germany /
Switzerland / France / Italy
Spain/ Portugal

Central & Eastern Europe
Finland / Estonia / Latvia /
Lithuania / Russia / Belarus
Romania / Bulgaria / Ukraine /
Poland / Serbia / Turkey

North America
Canada
USA



Asia Pacific
Australia
South Korea, China
Taiwan, Philippines
India, Japan

Latin America
Argentina
Chile, Brazil
Mexico, Columbia
Guatemala, Peru

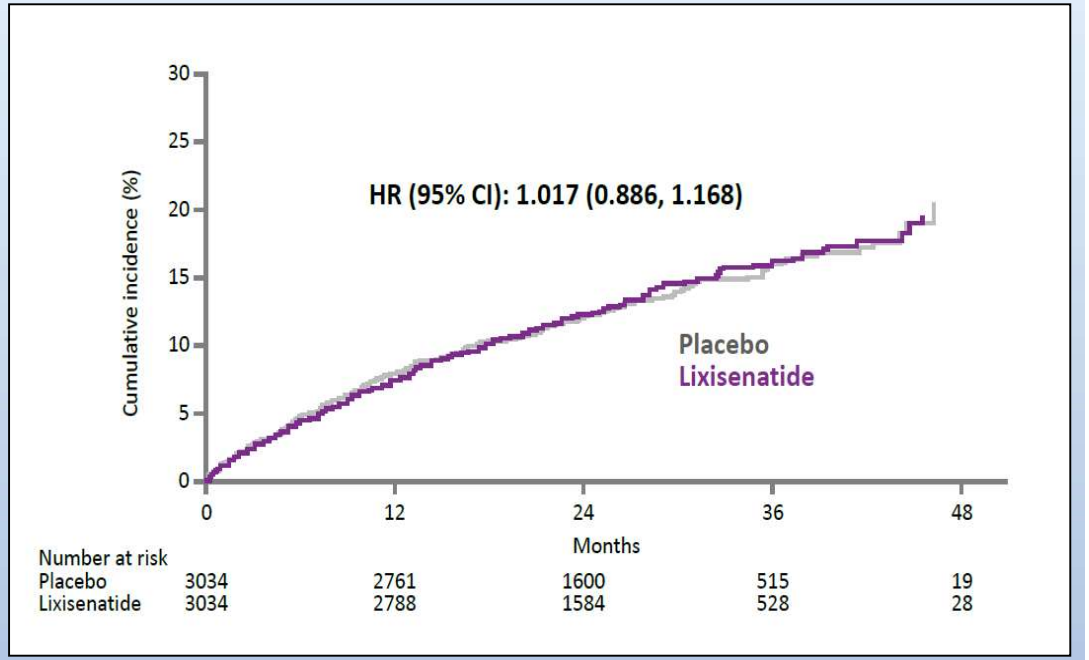
Middle East & Africa
Egypt, Tunisia, UAE,
Israel. South Africa

Studio ELIXA (Evaluation of LIXisenatide in Acute Coronary Syndrome)

Risultati endpoint primario/tempo al 1° evento per ciascun componente individuale dell'endpoint primario

Prof. S. Del Prato:
«Lo studio Elixa è il primo studio di outcome cardiovascolare per quanto riguarda gli agonisti del recettore del GLP-1 e conferma la sicurezza dell'impiego di lixisenatide anche nei soggetti con diabete tipo 2 ad alto rischio di eventi cardiovascolari. L'Italia ha partecipato in modo attivo alla conduzione e conclusione di questo importante trial clinico, confermando l'eccellenza della diabetologia italiana e contribuendo a rafforzare la collaborazione con i cardiologi. Studi di questa portata (6000 pazienti seguiti per oltre 4 anni) rappresentano la base per un impiego dei farmaci per il controllo della glicemia sempre più basato sull'evidenza….»

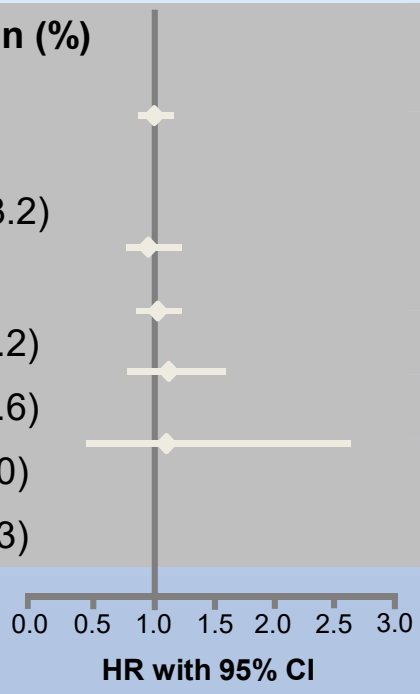
Endpoint primario composito



Poiché il limite superiore dell'intervallo di confidenza al 95% a due code dell'endpoint I era inferiore al margine pre-specificato di non inferiorità di 1.3, la non-inferiorità di lixisenatide vs placebo è stata dimostrata.

Tempo al primo evento per ciascun componente individuale dell'endpoint primario

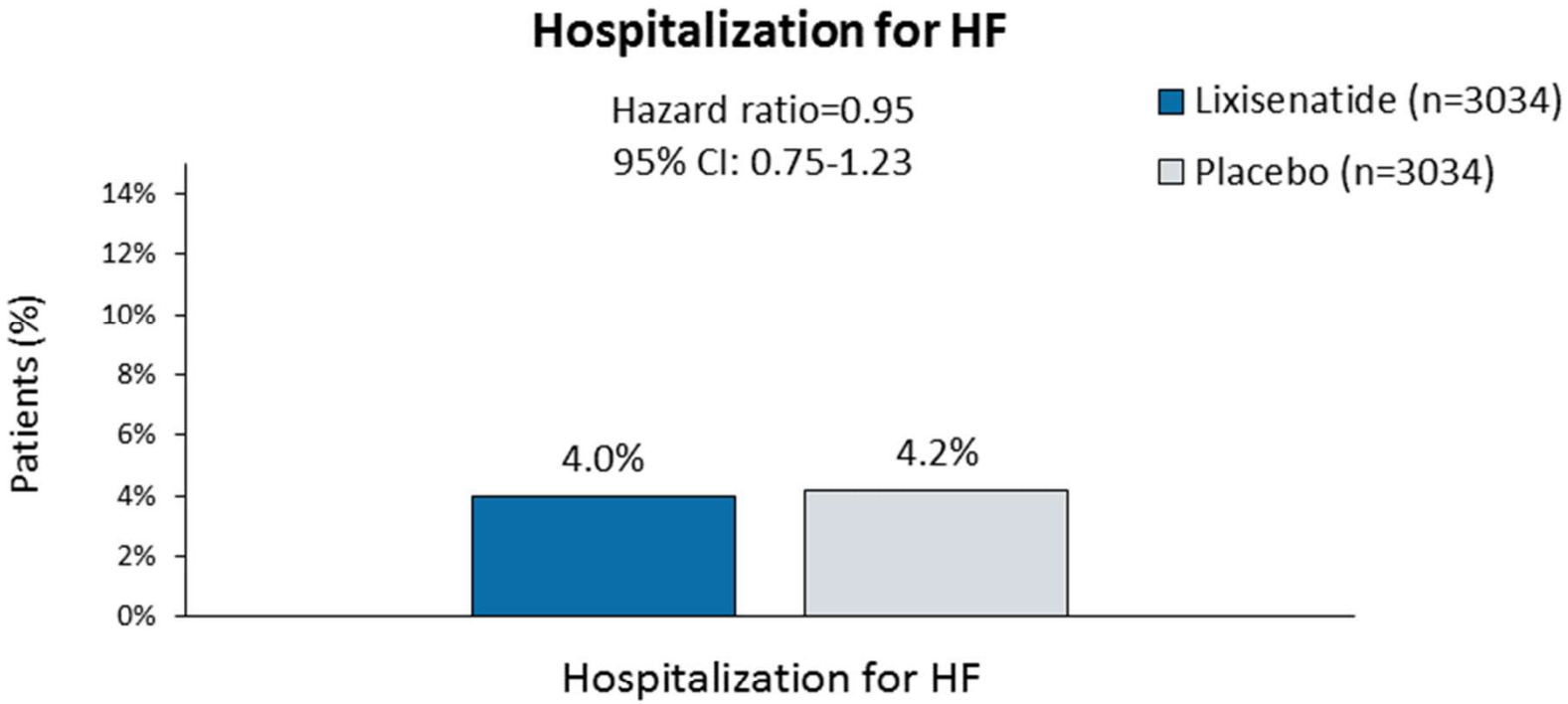
	Lixisenatide, n (%)	Placebo, n (%)	HR	95% CI
Composite of CV death, non-fatal MI, non-fatal stroke, or hospitalization for UA	406 (13.4)	399 (13.2)	1.02	0.89, 1.17
CV death	156 (5.1)	158 (5.2)	0.98	0.78, 1.22
MI	270 (8.9)	261 (8.6)	1.03	0.87, 1.22
Stroke	67 (2.2)	60 (2.0)	1.12	0.79, 1.58
Hospitalization for UA	11 (0.4)	10 (0.3)	1.11	0.47, 2.62



Endpoint CV singoli: la frequenza di ciascuno era simile nei due gruppi

Pfeffer MA et al. NEJM 2015;373:2247–57

ELIXA: Hospitalization for HF



Pfeffer M, et al. ADA 2015. Session 3-CT-SY28.

Evaluation of LIXisenatide in Acute Coronary Syndrome
Risultati & conclusioni

Lixisenatide **ha raggiunto il criterio pre-specificato di non inferiorità vs il gruppo placebo per l'endpoint primario composito** di morte CV, infarto del miocardio non fatale, ictus non fatale, o ospedalizzazione per angina instabile

Lixisenatide ha mostrato un consistente effetto neutrale su ciascun componente individuale dell'endpoint primario composito e degli endpoint CV secondari

Lixisenatide non ha aumentato il rischio di insufficienza cardiaca
Differenza statisticamente non significativa per la frequenza di ospedalizzazione per scompenso cardiaco
(hazard ratio, 0.96; 95% CI, 0.75 to 1.23)
o per l'incidenza di morte per cause cardiovascolari
(hazard ratio, 0.94; 95% CI, 0.78 to 1.13

Lixisenatide rispetto a placebo:
Ha ridotto il peggiornamento dell'albuminuria
Non ha aumentato il rischio di ipoglicemia grave
Non ha aumentato il rischio di pancreatite o di carcinoma pancreatico

Cardiovascular Effect of Incretin-Based Therapy in Patients withType 2 Diabetes Mellitus: Systematic Review and Meta Analysis

Una recente metanalisi ha confermato la sicurezza cardiovascolare delle terapie con incretino-mimetici, ma non ha dimostrato un effetto di protezione cardiovascolare di queste terapie in particolare nei pazienti a basso rischio cardiovascolare

J.T.Kim, S.Yang, J.I.Lee, M.J.Chang
PLOSONE|DOI:10.1371/journal.pone.0153502 April14,2016

Diabete tipo 2, studio LEADER

(Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results —A Long Term Evaluation)

Trial multicentrico internazionale iniziato nel 2010, nel quale sono stati seguiti per 5 anni 9340 adulti con diabete di tipo 2 ad alto rischio, trattati con liraglutide oppure un placebo, in aggiunta al trattamento standard.

- Minor rischio di eventi cardiovascolari maggiori con liraglutide

La liraglutide riduce in modo significativo il rischio di eventi avversi cardiovascolari maggiori, e ciò vale per tutti e tre i componenti dell'endpoint primario:

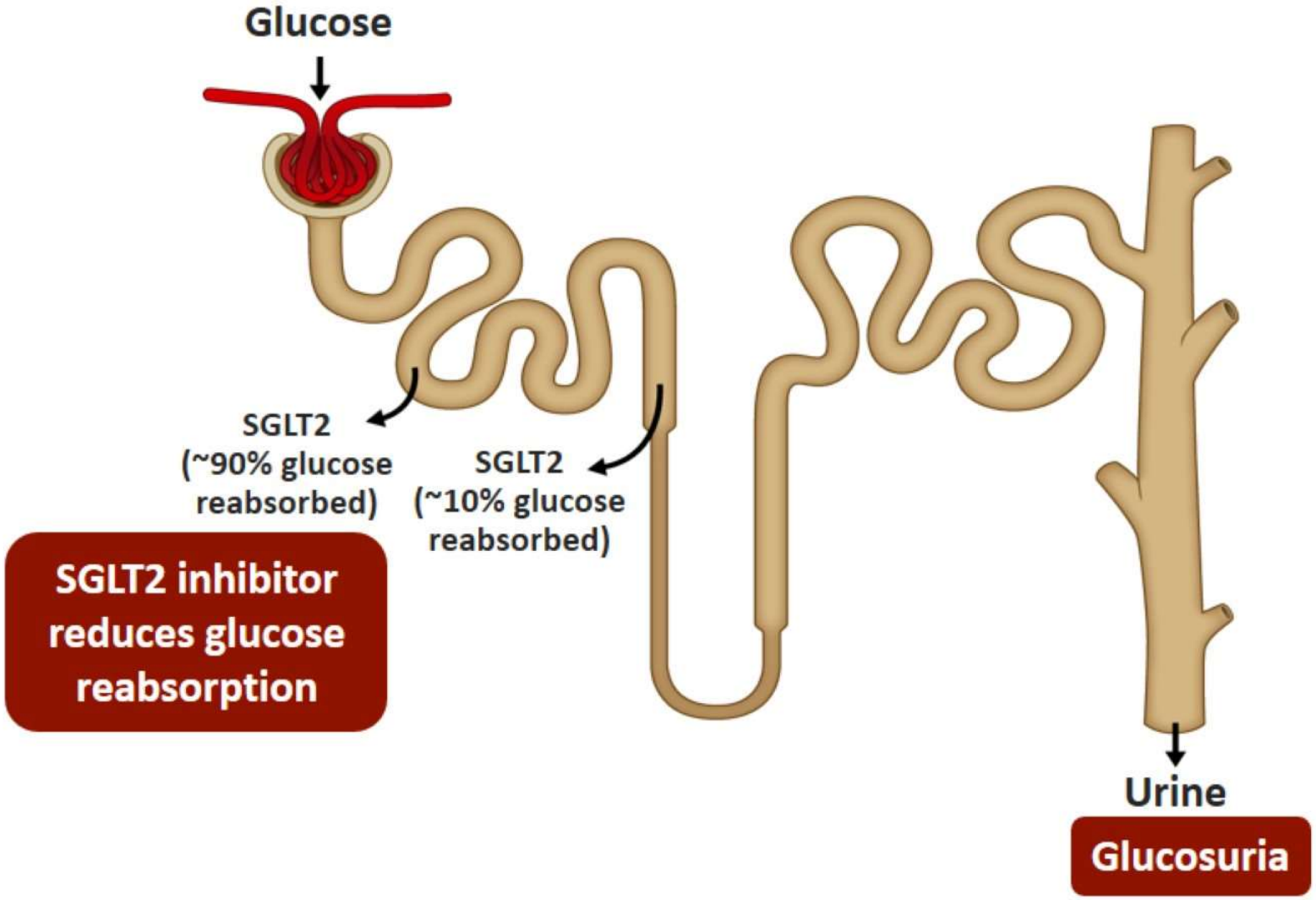
1. **decesso per cause cardiovascolari,**
2. **infarto miocardico non fatale,**
3. **ictus non fatale**

I dati completi dello studio saranno presentati in giugno in occasione del meeting annuale dell'American Diabetes Association (ADA)

http://www.pharmastar.it/popup/stampa.html?idlink=20847

SGLT2 Inhibitors

MOA



Nauck MA. *Drug Des Devel Ther*. 2014;8:1335-1380.[2]

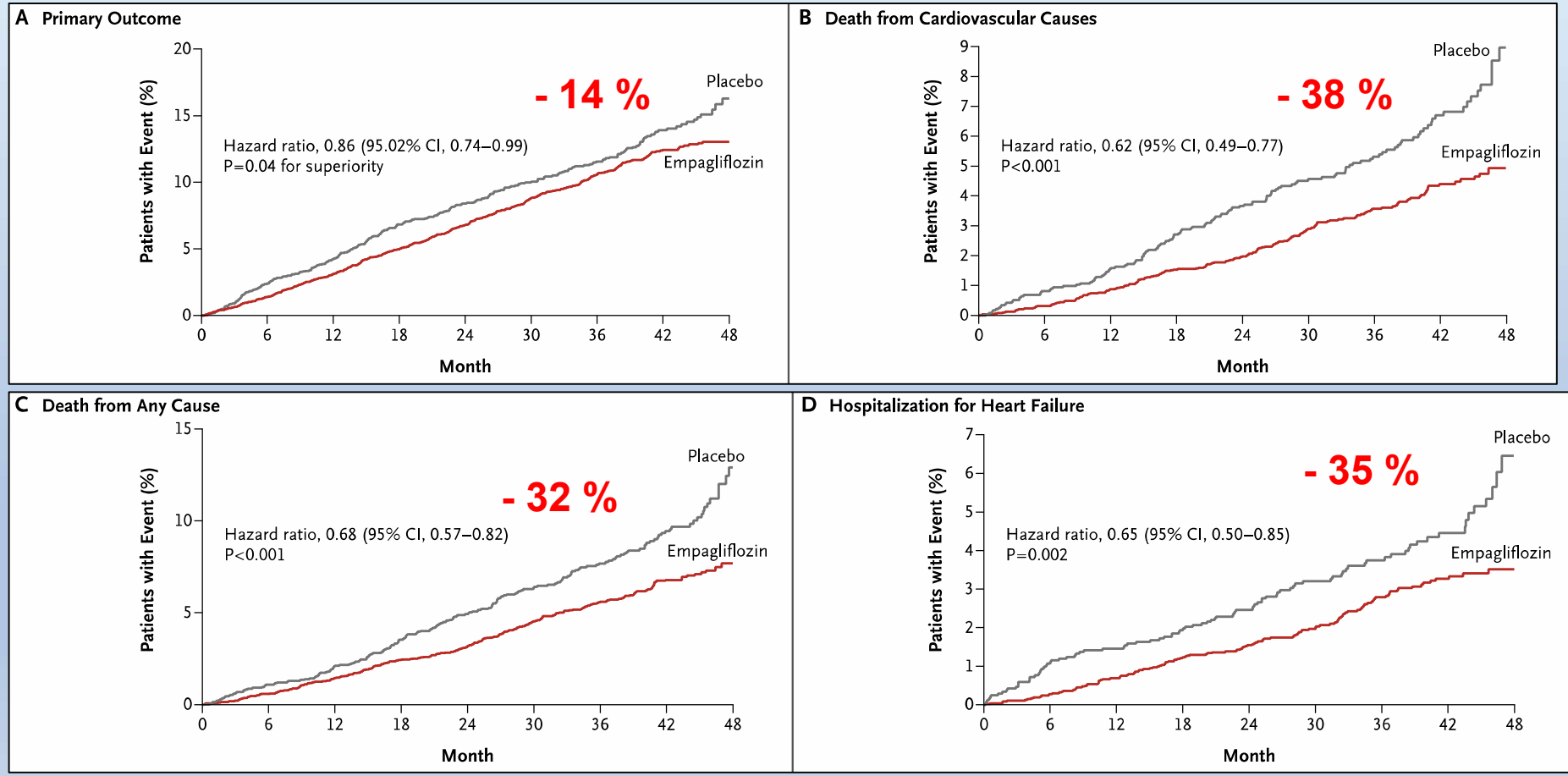
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

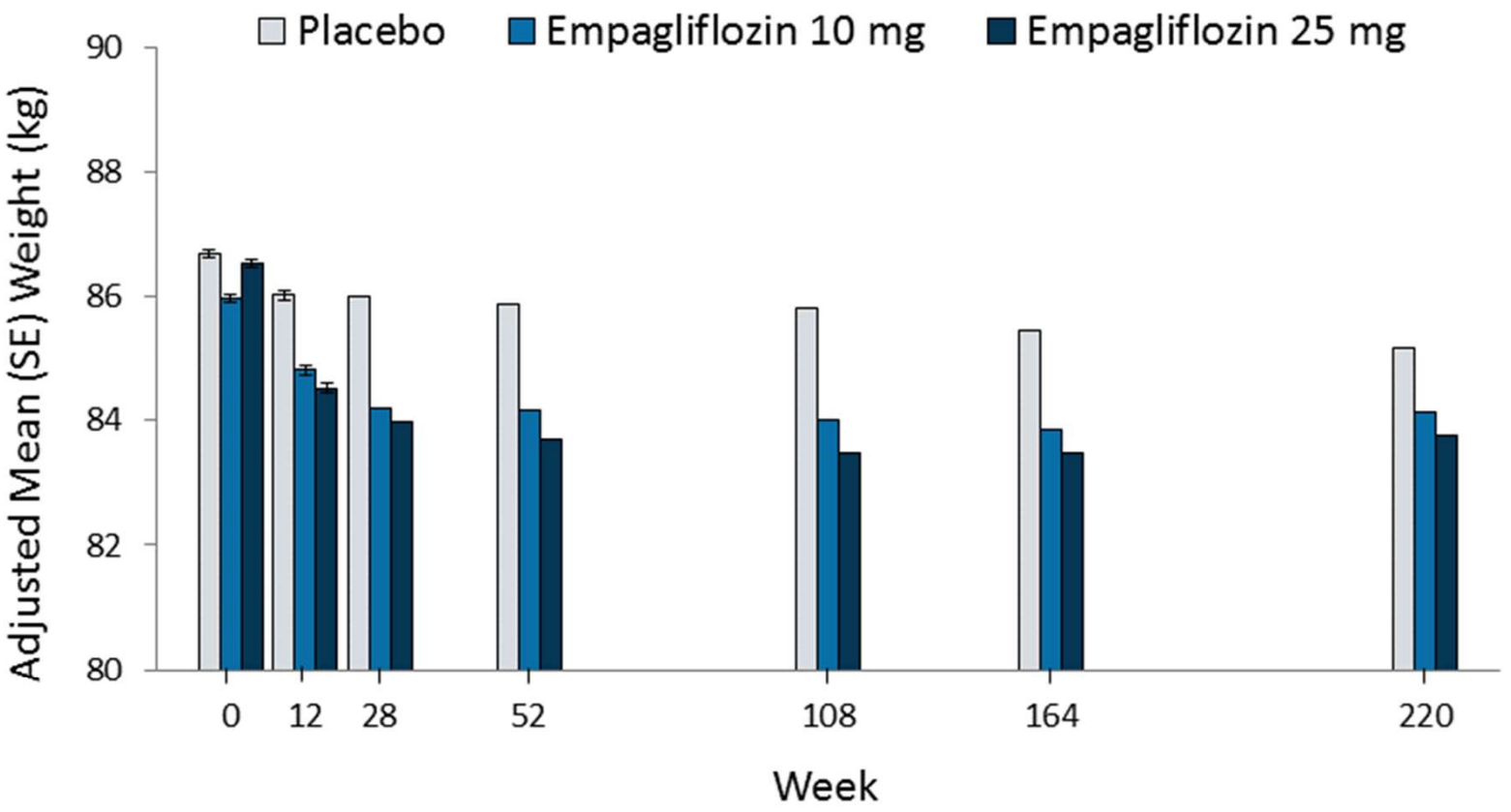
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

EMPA-REG

Pz 7020 pz follow up 3.1 a



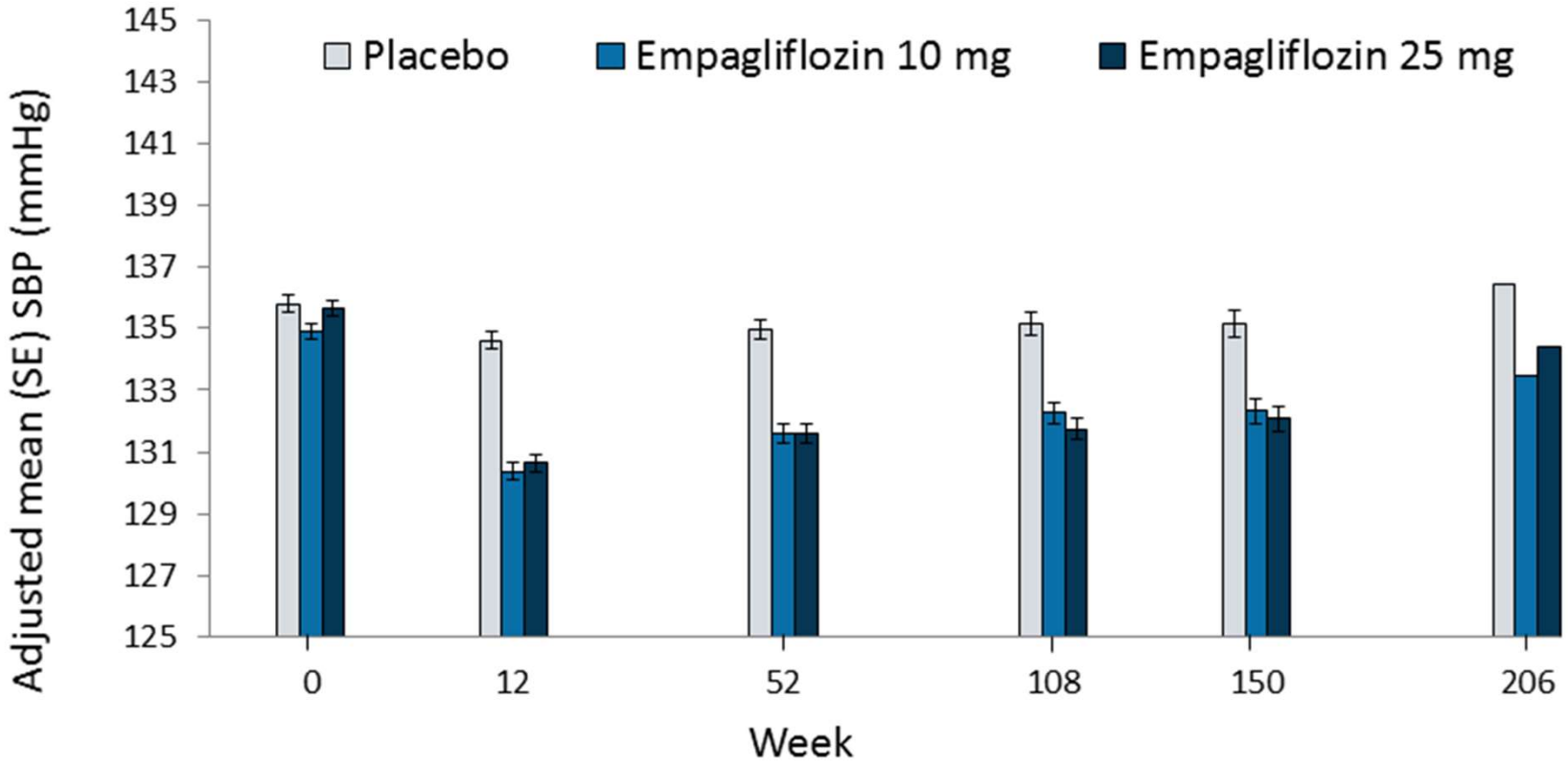
EMPA-REG OUTCOME: Body Weight



2 Kg

Zinman B, et al. *N Engl J Med*. 2015 Sep 17. [Epub ahead of print]

EMPA-REG OUTCOME: SBP

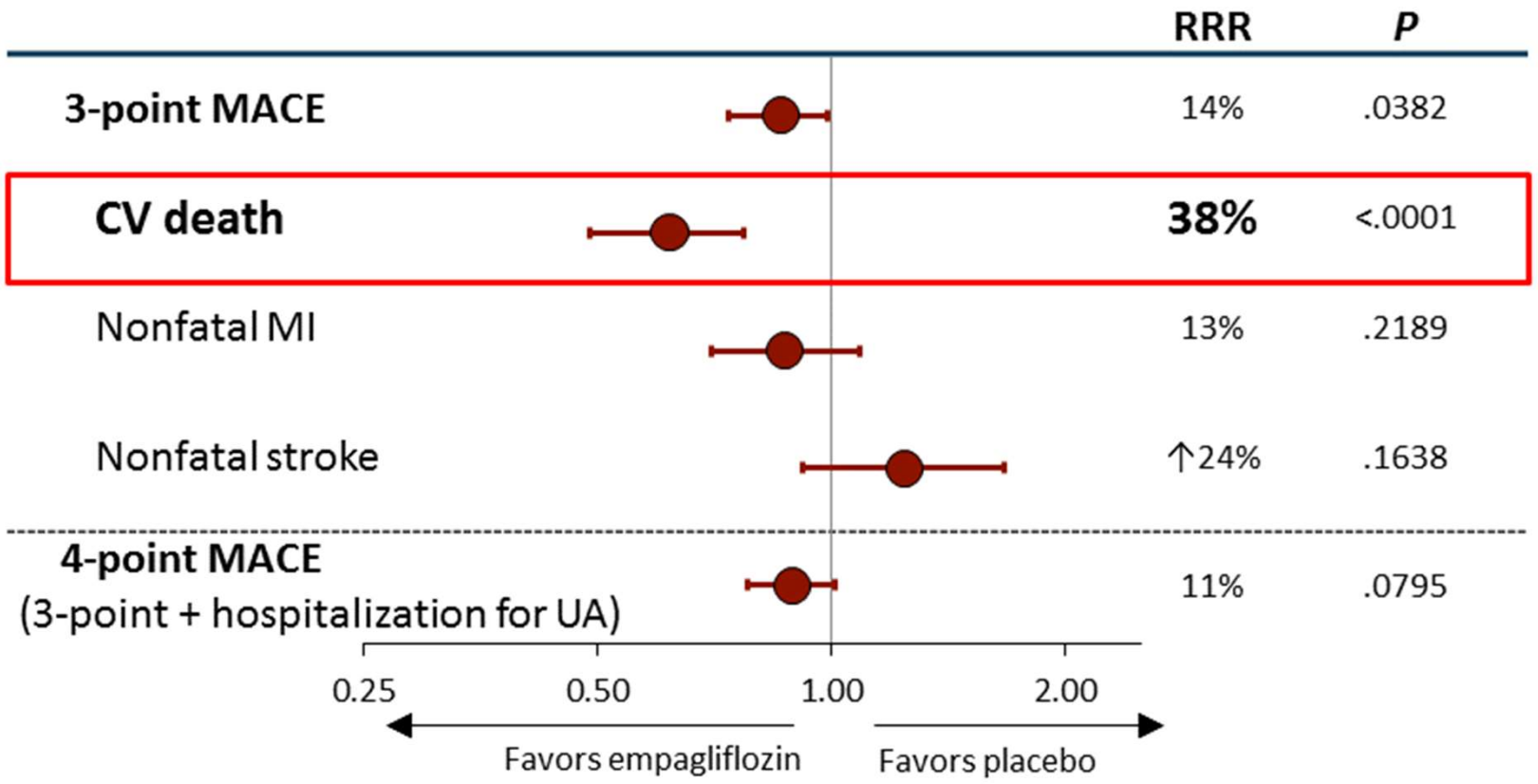


4 mmHg SBP

Zinman B, et al. *N Engl J Med*. 2015 Sep 17. [Epub ahead of print]

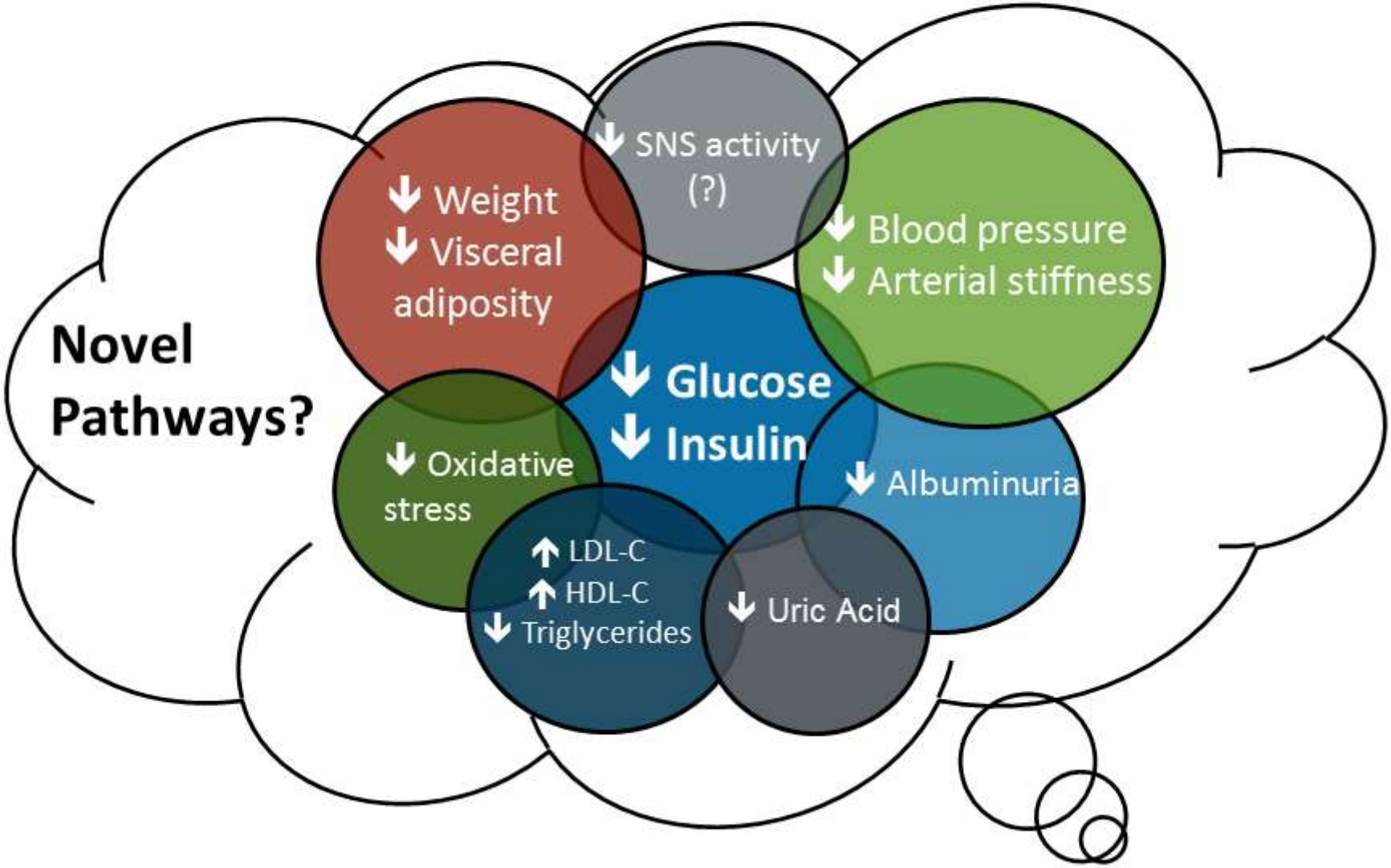
EMPA-REG OUTCOME: Effect of Empagliflozin vs Placebo on Individual CV Endpoints

CV Death, Nonfatal MI, or Nonfatal Stroke



Zinman B, et al. *N Engl J Med*. 2015 Sep 17. [Epub ahead of print]

Evidence SGLT2 Inhibitors Modulate a Range of Factors That Are Related to CV Risk



Inzucchi S, et al. *Diab Vasc Dis Res.* 2015;12:90-100.

Vi ringrazio per l’attenzione